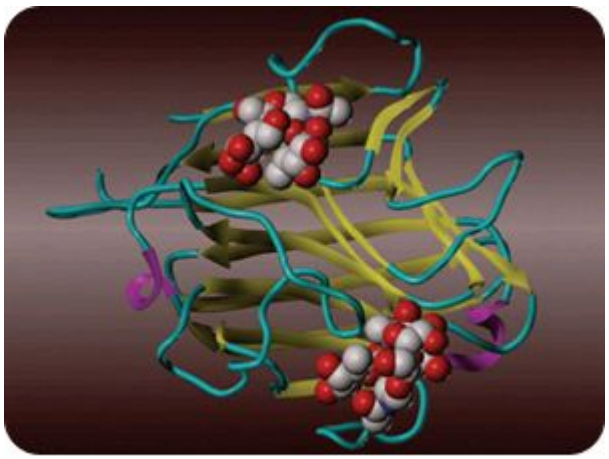
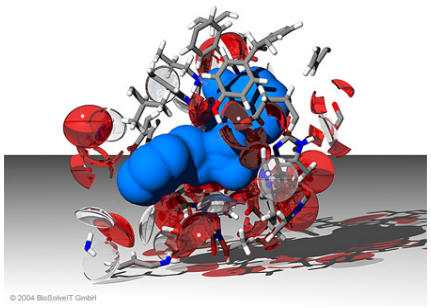


III KONWERSATORIUM CHEMII MEDYCZNEJ

LUBLIN

20-22 września 2010



Polskie Towarzystwo Chemii Medycznej

Uniwersytet Medyczny w Lublinie

Marszałek Województwa Lubelskiego

Katedra i Zakład Syntezy i Technologii Chemicznej Środków Leczniczych
Wydział Farmaceutyczny
Uniwersytet Medyczny w Lublinie
Autor: dr hab., prof. UM Dariusz Matosiuk

Lublin, 2010

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mgr Tomasz Wróbel

mgr Marcin Hus

Plan Konwersatorium

Poniedziałek, 20.09.2010

15.00-16.00 – Rejestracja Uczestników

16.00-16.30 - Otwarcie Konwersatorium

Prof. dr hab. Dariusz Matosiuk,

Prof. dr hab. Andrzej Książek JM Rektor, Uniwersytet Medyczny w Lublinie;

16.30-17.15 – Wykład Inauguracyjny _ 1

Polish-Norwegian Research Fund PNRF-103-AI-1/07 www.cns-platform.eu

Prof.Ingebrigt Sylte, Univeristy of Tromsø, Norway

„ Molecular modelling of drug targets."

17.15-18.00 – Wykład Inauguracyjny _ 2

Prof. William L. Scott, IU-PU, Indianapolis, USA

„ Distributed Drug Discovery (D3): linking basic research and education to find drug leads for neglected diseases."

18.30-22.00 – Spotkanie powitalne

Wtorek, 21.09.2010

9.30-11.00 – Sesja wykładowa – Sesja z programu Polsko-Norweskiego Funduszu Badań Naukowych.

Polish-Norwegian Research Fund PNRF-103-AI-1/07 www.cns-platform.eu

Prowadzący sesję – prof. dr hab. Janina Karolak-Wojciechowska, prof. dr hab. Zdzisław Chilmonczyk

L-1

Dr Joanna Wierońska,Instytut Farmakologii PAN, Kraków,

„ Matabotropic glutamate receptors as a target for novel antidepressant and anxiolytic drugs."

L-2

Dr Aina W. Ravna, University of Tromsø, Norway

„ Homology modelling of neurotransmitter transporters."

L-3

Mgr Rafał Kurczab, Instytut Farmakologii PAN, Kraków

„ Virtual Screening approach as a potent technology an drug design campaigns. Methods, applications and computational perspectives."

11.00-11.30 – przerwa na kawę

11.30-13.00 – Komunikaty – Sesja z programu Polsko-Norweskiego Funduszu Badań Naukowych.

Polish-Norwegian Research Fund
PNRF-103-AI-1/07 www.cns-platform.eu

Prowadzący sesję – prof. dr hab. Katarzyna Kieć-Kononowicz, dr hab. Andrzej Bojarski

K-1

Dr Mari Gabrielsen, university of Tromsø, Norway

„Ligand interactions and ligand-induced conformational states of the serotonin transporter."

K-2

Dr Małgorzata Jarończyk, Narodowy Instytut Leków, Warszawa

„Comparison of ligand docking to different SERT conformations."

K-3

Mgr Dawid Warszycki, Instytut Farmakologii PAN, Kraków

„ The implementation of an expert system to search for novel substances acting on serotonergic and glutamatergic systems."

K-4

Dr Agnieszka Polit, Uniwersytet Jagielloński, Kraków

" Fluorescent probes – types and applications."

13.00-14.00 – Lunch

14.00-15.30 – Sesja wykładowa – Alzheimer

Prowadzący sesję – prof. dr hab. Barbara Malawska, prof. dr hab. Dariusz Matosiuk

L-4

Prof. dr hab. Jacek Kuźnicki, MIBMK, Warszawa

„ High throughput calcium screens for identification of potential drugs for Alzheimer's disease."

L-5

Prof. dr hab. Andrzej Stepulak, Uniwersytet Medyczny, Lublin

„ Intracellular signaling in Alzheimer disease. "

L-6

Dr Marta Wiśniewska, IMBMK, Warszawa

„ Role of LEF1/beta-catenin complex in regulation of gene transcription in the adult brain. "

15.30-16.00 – Przerwa na kawę

16.00-17.30 – Sesja posterowa i prezentacje ustne posterów

Prowadzący sesję – dr hab. Zofia Mazerska,
prof. dr hab. Andrzej Lipkowski,

PP-1

Mgr Monika Szuster, Uniwersytet Medyczny, Lublin

„ The novel derivatives of methylpiperazine and 4-methylhistamine with moderate affinity for H_4R."

PP-2

Dr Anna Czopek, CMUJ, Kraków

„ RP-TLC determination of the lipophilicity of N-4-arylpiperazin-1-yl-propyl- imidazolidine-2,4-dione and pyrrolidine-2,5-dione."

PP-3

Mgr Gniewomir Latacz, CMUJ, Kraków

„ Chiral and specific activity of immobilized, recombinant D-hydantoinase towards racemic phenyl ring substituted 5-benzylhydantoin derivatives."

PP-4

Mgr Michalina Ignasik, CMUJ, Kraków

„ Novel dual binding site cholinesterases inhibitors with phthalimide moiety."

PP-5

Dr Krzysztof Kamiński, CMUJ, Kraków

„ Synthesis and anticonvulsant activity of new N-[4-(arylpiperazin-1-yl)]-(3,3-dimethyl-2,5-dioxopyrrolidin-1-yl)- and (3,3-ethyl-2,5-dioxo-pyrrolidin-1-yl)- acetamides."

PP-6

Stud. Sebastian Lijewski, Uniwersytet Medyczny, Poznań

„ Photochemical properties of novel porphyrazines and phthalocyanines possessing peripheral fluorine substituents as potential photosensitizers in photodynamic therapy."

Środa, 22.09.2010

9.30-11.00 – Sesja wykładowa – Nowe trendy.

Prowadzący sesję – prof. dr hab. Jan Mazerski,
prof. dr hab. Marek Cegła

L-7
Prof. dr hab. Ryszard Andruszkiewicz, Politechnika Gdańska
„ The future of antibiotics."
L-8
Prof. dr hab. Andrzej Lipkowski, CMDiK PAN, Warszawa
"Multitarget medicines. Opioid-tachykinin chimeric peptides."
L-9
Dr hab. Katarzyna Kulig, CMUJ, Kraków
„ Chiral auxilaries in the synthesis of β-aminoalcohols."

11.00-11.30 – przerwa na kawę

11.30-13.00 – Sesja wykładowa – Między Teorią a Praktyką.

Prowadzący sesję – prof. dr hab. Aleksander P. Mazurek
prof. dr hab. Jacek Kuźnicki

L-10
Prof. dr hab. Jerzy Gębicki, Politechnika Łódzka
„ In search for new therapeutics: from basic research to the market products."
L-11
Prof. dr hab. Jarosław Polański, Uniwersytet Śląski, Katowice
" Mining databases for the exploration of the architecture of drugs."
L-12
Mgr Urszula Kijkowska-Murak,Uniwersytet Medyczny w Lublinie,
" Complex activity analysis for some 5-HT_{1A} receptor arylpiperazine ligands."

13.00-14.00 – Lunch

14.00-15.30 – Sesja posterowa i prezentacje posterowe

Prowadzący sesję – prof. dr hab. Jan Mazerski,
prof. dr hab. Jerzy Gębicki

PP-7
Mgr Paulina Kosikowska, Politechnika Wrocławska
„ Novel phosphonic and phosphinic acid derivatives as inhibitors of bacterial ureases."
PP-8
Mgr Tomasz Kościółek, Instytut Farmakologii PAN, Kraków
„ Application of structural interaction fingerprints (SIFt) in identification and analysis of GPCR binding-sites."

PP-9

Mgr Joanna Kozak, Uniwersytet Medyczny, Lublin

„ Biological activity of new derivatives of dextromethorphan as potent allosteric inhibitors of neuronal nicotinic receptors $\alpha 3\beta 4$."

PP-10

Mgr Jacek Kujawski, Uniwersytet Medyczny, Poznań

„ New fused and dimeric azahetarens with potential cytostatic activity."

PP-11

Dr Dorota Olender, Uniwersytet Medyczny, Poznań

„ Synthesis of new imidazofuroxan derivatives with potential biological activity."

PP-12

Mgr Grzegorz Satała, Instytut Farmakologii PAN, Kraków

" Verification of virtual screening results for 5-HT_6 receptor in in vitro experiments."

15.30-16.00 – Przerwa na kawę

16.00-18.00 – Komunikaty

Prowadzący sesję – prof. dr hab. Ryszard Andruszkiewicz ,
prof. dr hab. Jarosław Polański

K-5

Dr Beata Kolesińska, Polietchnika Łódzka

„Glycosylation of Peptides."

K-6

Prof. dr hab. Zbigniew Kamiński, Politechnika Łódzka

„ An approach for application of synthetic peptides as markers of autoimmune diseases."

K-7

Dr Ewa Szymańska, CMUJ, Kraków

" Studies on phenylalanine-based AMPA/KA receptor ligands."

K-8

Dr Mariusz Mojzych,Akademia Podlaska, Siedlce

" Synthesis and pharmacological evaluation of New sildenafil analogues."

K-9

Dr Agnieszka Markowska, Uniwersytet Medyczny, Białystok

“ Urokinaze inhibitors.”

19.30-23.00 – Wieczór pożegnalny „Nad Zalewem”

Lista prezentacji posterowych:

PP-1 Szuster Monika, mgr
The novel derivatives of methylpiperazine and 4-methylhistamine with moderate affinity for H_4R.

PP-2 Czopek Anna, dr
RP-TLC determination of the lipophilicity of N-4-arylpiperazin-1-yl-propyl-imidazolidine-2,4-dione and pyrrolidine-2,5-dione.

PP-3 Latacz Gniewomir, mgr
Chiral and specific activity of immobilized, recombinant d-hydantoinase towards racemic phenyl ring substituted 5-benzylhydantoin derivatives.

PP-4 Ignasik Michalina, mgr
Novel dual binding site cholinesterases inhibitors with phthalimide moiety.

PP-5 Kamiński Krzysztof, dr
Synthesis and anticonvulsant activity of new *N*-[4-(arylpiperazin-1-yl)]-(3,3-dimethyl-2,5-dioxopyrrolidin-1-yl)- and (3,3-ethyl-2,5-dioxopyrrolidin-1-yl)- acetamides.

PP-6 Lijewski Sebastian, stud.
Photochemical properties of novel porphyrazines and phthalocyanines possessing peripheral fluorine substituents as potential photosensitizers in photodynamic therapy.

PP-7 Kosikowska Paulina, mgr inż.
Novel phosphonic and phosphinic acid derivatives as inhibitors of bacterial ureases.

PP-8 Kościółek Tomasz, mgr
Application of structural interaction fingerprints (SIFt) in identification and analysis of GPCR binding-sites.

PP-9 Kozak Joanna, mgr
Biological activity of new derivatives of dextromethorphan as potent allosteric inhibitors of neuronal nicotinic receptors $\alpha 3\beta 4$.

PP-10 Kujawski Jacek, mgr
New fused and dimeric azahetarens with potential cytostatic activity.

PP-11 Olender Dorota, dr
Synthesis of new imidazofuroxan derivatives with potential biological activity.

PP-12 Satała Grzegorz, mgr
Verification of virtual screening results for 5-HT6 receptor in in vitro experiments.

P-1 Aletańska-Kozak Monika, dr
Synthesis and antibacterial activity of new benzylthiosemicarbazide derivatives.

P-2 Baran Marzena, mgr
Synthesis of benzimidazole, pyridone and teophylline derivatives' and their biological activity.

P-3 Bednarczyk-Cwynar Barbara, dr
Oleanolic acid morpholide oximes acylation as a method of synthesis of highly effective MDR inhibitors.

P-4 Bednarczyk-Cwynar Barbara, dr
Nicotinic acid derivatives of some triterpenes as highly effective antiviral compounds.

P-5 Bielawska Anna, dr hab.
Studies on the interactions between DNA topoisomerases and PAMAM-NH_2 dendrimer –modified digoxin and proscillaridin A conjugates.

P-6 Bielawski Krzysztof, dr hab.
The effect of dinuclear platinium(II) complex on cell signalling pathways in human breast cancer cells.

P-7 Chlebek Iwona, mgr
Synthesis, anticonvulsant activity and 5-HT_{1A}, 5-HT_{2A} receptor affinity of new N-(4-arylpiperazin-1-yl)-propyl- derivatives of 3,3-disubstituted pyrrolidine-2,5-dione.

P-8 Chorąży-Jakubowska Anna, mgr
Application of Mitsunobu reaction for the synthesis of various substituted 4-amino-1-benzylpiperazine derivatives.

P-9 Cytarska Joanna, dr
New isophosphoramide mustard analogues as prodrugs for gene therapy.

P-10 Dela Anna, mgr
5-HT_{1A} serotonin receptors affinity of methoxybenzylidene derivatives of hydantoin.

P-11 Dela Anna, mgr
Influence of the methoxy substituent(s) of arylidenehydantoin derivatives on their affinity to α_1-ARs.

P-12 Dymek Anna, mgr
Evaluation of mutagenic properties of some triazine derivatives, ligands of histamine H_4 receptor, using *Vibrio harveyi* test.

P-13 Gunia Agnieszka, mgr
Preliminary antiepileptic activity evaluation for some 6-methoxyxantone derivatives.

P-14 Guzior Natalia, mgr
N-benzyl substitiuted 2-(4-(diphenylmethylene)piperidin-1-yl)-4-hydroxybutanamides as a potential GABA uptake inhibitors.

P-15 Handzlik Jadwiga, dr
5-Hydantoin derivatives as potential efflux pump inhibitors.

P-16 Handzlik Jadwiga, dr
Synthesis and mutagenic properties of new hydantoin derivatives with potential anti-MDR activity.

P-17 Kalembkiewicz Elżbieta, mgr
Synthesis and evaluation of potential mono- and bivalent ligands of adenosine A_{2A} receptors.

P-18 Kapustikova Iva, mgr
Determination of pK_a using ^{1}H NMR spectroscopy and capillary zone electrophoresis.

P-19 Kapustikova Iva, mgr
Thermodynamics of partitioning of potential drugs into water/octanol and water/cyclohexane solvent systems.

P-20 Karcz Tomasz, mgr
Stable expression of fluorescently tagged A_{2A} adenosine receptor in HEK 293 cells.

P-21 Karczmarzyk Zbigniew, dr hab.
The structural characterization of 2-{2-[4-(2-fluorophenyl)-piperazin-1-yl]ethyl}-5,7-dimethyl-6-phenyl-1,2,3,4-tetrahydro-6*H*-pyrrolo[3,4-*d*]pyridazine-1,4-dione, new potential analgesic agent.

P-22 Kasprzak Maria, mgr
In vitro cytotoxic properties of two novel flavonone-based ruthenium complexes.

P-23 Kieć-Kononowicz Katarzynba, prof. dr hab.
Antiparkinsonian effects of novel adenosine A_{2A} receptor antagonists.

P-24 Koczorowski Tomasz, stud.
Synthesis and X-ray studies of novel porphyrazines possessing peripheral pyrrolyl and dimethylamino groups.

P-25 Kryjewski Michał, mgr
Synthesis, photophysical properties and photocytotoxicity of phthalocyanines possessing non-peripheral ester-alkyloxy substituents.

P-26 Kubas Karolina, mgr inż.
The polyphenol glycosides having calcium complexing properties.

P-27 Kuder Kamil, mgr
Docking of para-*t*-pentylphenoxyalkyl piperidine derivatives and fluorescent H_3 receptor Ligand KF-1 to histamine H_3 receptor homology model.

P-28 Ligęza Agnieszka, mgr
Optimisation of dextromethorphane N-demethylation process.

P-29 Lijewski Sebastian, stud.
Synthesis, characteristics and optical sensor property of novel porphyrazines possessing bulky peripheral thiol substituents.

P-30 Łażewska Dorota, dr
Convenient way of synthesis and crystal structure of JNJ 7777120.

P-31 Maniukiewicz Waldemar, dr inż.
Polimorphism of the pharmaceutical substances on the example of Imatinibe® mesylate.

P-32 Markowska Agnieszka, dr
Potential peptidic urokinaze inhibitors.

P-33 Mikuś Michał, stud.
Physical properties of porphyrazines possessing in the core the following cations Mg^{2+}, Zn^{2+}, Cu^{2+}, Mn^{3+}, Fe^{3+}.

P-34 Mordalski Stefan, mgr.
Application of highly efficient database systems in virtual screening protocol.

P-35 Mrozek Agnieszka, dr inż.
Analysis of the docking process of triazine derivatives of the nitrogen iperite with confirmed antitumor activity to the binding cavities of the library of artificial receptors.

P-36 Nowaczyk Alicja, dr
The 1-[3-(4-arylpiperazin-1-yl)propyl]pyrrolidin-2-one derivatives as antiarrhythmic agents: a QSAR studies.

P-37 Nowak Magdalena, stud.
Synthesis and photochemical characteristics of novel norphthalocyanine possessing peripherally annulated perhydrodiazepine ring.

P-38 Obniska Jolanta, dr hab.
Design, synthesis and anticonvulsant activity of new N–Mannich bases derived from 3-phenyl-pyrrolidine-2,5-dione.

P-39 Oracz Monika, mgr inż.
Evidence for polymorphism of zolendronic acid monohydrate.

P-40 Owczarzak Kamil, stud.
Structure determination of novel porphyrazines possessing peripheral 2,5-dimethyl-pyrrolyl and dimethylamino groups using computational methods and infrared - Raman spectroscopy.

P-41 Płazińska Anita, mgr
Molecular docking study of stereoisomers of fenoterol derivatives to the β_2 adrenergic receptor and molecular dynamic simulations for selected agonist- β_2-AR complexes.

P-42 Prymula Katarzyna, mgr
New strategy for use of pharmacophore models in virtual screening for 5-HT_6 receptor ligands.

P-43 Różański Jakub, dr
ABDO: source of new cytostatics.

P-44 Sobotta Łukasz, mgr
Photochemical assessment of pyrrole porphyrazines as potential PDT agents.

P-45 Stefański Tomasz, dr
Synthesis and biological evaluation of *trans*-methylthiostilbene derivatives – potential chemopreventive and chemiotherapeutic agents.

P-46 Szacoń Elżbieta, dr
Synthesis of new 1-(1-arylimidazolidyn-2-ylideno)-3-aminosulfonylurea derivatives.

P-47 Szczesio Małgorzata, dr inż.
Crystal structures of aryldithiocarbazonics showing tuberculostatic activity.

P-48 Szymańska Ewa, dr
Synthesis and structure of urea derivatives of hydantoin.

P-49 Targowska-Duda Katarzyna, mgr
Computational modeling of interactions between nicotinic acetylcholine receptor and different classes of allosteric modulators.

P-50 Tengler Jan, dr
Synthesis of fluorinated aryloxypropanol analogues as potential adrenoreceptore blocking agents.

P-51 Tengler Jan, dr
Preparation of 3-alkylamino-2-hydroxypropyl-4-(2-alkoxyethoxy) benzoates.

P-52 Waszkielewicz Anna, dr
Microbiological *Cunninghamella* model for metabolism assay of antiepileptic drug candidates.

P-53 Więcek Małgorzata, dr
The influence of aromatic substituent in position 6 of 4-(4-methylpiperazin-1-yl)-1,3,5-triazin-2-amine derivatives on histamine H_4 receptor affinity.

P-54 Zagórska Agnieszka, dr
Determination of the lipophilicity of arylpiperazynylalkyl derivatives of imidazo[2,1-f]-theophylline by RP HPLC.

P-55 Zajdel Paweł, dr
Solid-phase synthesis of sulfonamide derivatives of differently substituted alkylamines in the search for CNS receptor ligands.

P-56 Zavyalova Olga, dr
Kinetic study of thymidine and uridine radiolysis.

P-57 Żwawiak Justyna, mgr
Reactions of nucleophilic substitution in bicyclic nitroimidazodihydrooxazoles.

P-58 Żylewski Marek, dr
Attempt for use of the NMR spectroscopy in measurement of the chemicals lipophilicity .

P-59 Urniaż D. Rafał, mgr
The appliance of the extrapolation methods used in biological research to create a pharmacokinetic model of medicaments isolated from plants on example of codeine.

P-60 Pająk Karolina, mgr
Development of *N*-acryloxysuccinimide-based monoliths with controlled reactivity for analytical applications.

WYKŁADY

IL-1

Polish-Norwegian Research Fund
PNRF-103-AI-1/07 www.cns-platform.eu

Molecular Modelling of Drug Targets.

Ingebrigt Sylte, Kurt Kristiansen, Aina W. Ravna, Mari Gabrielsen, Inger Lindin, Yimingjiang Wuxiuer, Svein G. Dahl

Medical Pharmacology and Toxicology, Department of Medical Biology, Faculty of Health Sciences, Universitym of Tromsø, N-9037 Tromsø, Norway
e-mail: ingebrigt.sylte@uit.no

Structural knowledge of drug targets is essential for the understanding of how drugs interfere with cellular communication and regulation. When the structure of the drug target is known, computational chemistry methods can be used to study ligand - target binding affinities and to search for new putative binders using virtual screening protocols. The protein targets for drug action can be broadly divided into receptors, ion channels, enzymes and transporter/carrier proteins. Membrane proteins like receptors and transporter proteins are involved in many different cellular mechanisms and provide a variety of targets for pharmacological intervention. Membrane proteins are therefore among the most interesting macromolecules from a structural point of view. However, such protein structures are difficult to study by traditional experimental methods, and of more than 66.000 structural entities present in the PDB database only around 1200 are of membrane proteins. The lack of detailed experimental structures limits the design of new ligands interfering with membrane proteins. In the lack of experimental structure protein homology modelling is an approach for generating structural models of interesting membrane proteins.
The molecular modelling research group is using molecular modelling techniques in combination with experimental techniques to gain insight into structure, function and ligand interactions of drug target proteins. The main drug targets for our studies during the last years have been receptors and transporters in the CNS, zinc metalloproteinases (thermolysin-like enzymes) and enzymes of the family of short chain alchol dehydrogenases/reductases. Homology modelling is used to construct 3D protein models of membrane proteins. Models of membrane proteins and experimentally generated 3D structures of enzymes are used to study ligand –target binding affinities by automatic docking and molecular dynamics (MD) simulations based prediction methods. MD simulations are also used to study time dependent structural changes following protein-drug or protein-protein complexation. Virtual ligand screening protocols are used to indentify putative new drug target binders.

The studies are partly supported by a grant PNRF-103-AI-1/07 from Norway through the Norwegian Financial Mechanism.

IL-2

Distributed Drug Discovery (D3): Linking Basic Research and Education to Find Drug Leads for Neglected Diseases.

William L. Scott

Department of Chemistry and Chemical Biology,
Indiana University-Purdue University, Indianapolis, Indiana 46202, USA
e-mail: wscott@chem.iupui.edu

This presentation will discuss the concept of Distributed Drug Discovery (D3) and how it adapts basic research to enable, on a global scale, the simple, reproducible and inexpensive synthesis of many potential drug-lead molecules for neglected diseases. D3 has created and published open-source virtual catalogs containing biomimetic molecules accessible by synthesis in academic laboratories across the world. We have demonstrated that students in Indianapolis, Moscow, Barcelona and Lublin can successfully carry out the synthetic procedures required to make these molecules. When computational collaborators access virtual catalogs their analysis can identify drug-lead candidates to synthesize. These molecules can then be readily made by undergraduate or graduate students, across the globe, in a distributed fashion. Currently molecules synthesized by students at IUPUI are being sent to the National Institutes of Health for screening by their academic network. Our collaborators in Kraków are helping D3 begin to connect synthesis with biological evaluation in a student setting. This open-source, integrated process of Distributed Drug Discovery facilitates a direct link between education and drug lead discovery for neglected diseases.

L-1

Polish-Norwegian Research Fund
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Metabotropic Glutamate Receptors as a Target for Novel, Antidepressant and Anxiolytic Drugs.

Joanna M. Wierońska, Piotr Brański, Katarzyna Stachowicz, Andrzej Pilc

Department of Neurobiology, Institute of Pharmacology,
Polish Academy of Science, Smętna 12, 31-343 Kraków
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Mental disorders, such as depression and anxiety, has become a large medical and social problem recently. Studies performed in animal tests and early clinical investigations brought a new insight in the pharmacotherapy of these disorders. Latest investigations are focused not only on monoaminergic neurotransmission, which constitutes only several percent of all in the brain, but mainly on the glutamatergic system, a main excitatory amino acid neurotransmitter, which constitutes more than 50% of all the neurotransmission. Eight types of metabotropic glutamate receptors (mGlu), divided into three groups according to sequence homology, pharmacology and the second messenger system they activate, seem to be excellent therapeutic tool. Localized on nerve terminals, post-synaptic sites and glial cells they can influence and modulate the action of glutamate on different levels in the synapse. Evidence indicate that pathophysiology of depression and anxiety is strongly dependent on the activity of glutamatergic system, therefore it is not surprising that mGlu receptors ligands have excellent antidepressant and anxiolytic effects. Recent advances in the identification of selective and specific compounds (both ortho- and allosteric ligands), and the generation of transgenic animals enabled to have new insight into the pathophysiology and therapy of mood disorders. At present, the most potent seem to be negative allosteric modulators of the first group (mGlu1 and mGlu5), and positive allosteric modulators of the second (mGlu2 and mGlu3) and third (mGlu4/7/8) group of mGlu receptors.

Acknowledgements

The study was partly supported by a grant PNRF-103-AI-1/07 from Norway through the Norwegian Financial Mechanism

L-2

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Homology Modelling of Neurotransmitter Transporters.

Aina W. Ravna [a], *Mari Gabrielsen* [a], *Małgorzata Jarończyk* [b], *Kurt Kristiansen* [a], *Svein Dahl* [a], *Zdzisław Chilmonczyk* [b], *Andrzej J. Bojarski* [c], *Ingebrigt Sylte* [a]

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The dopamine (DAT), serotonin (SERT) and noradrenalin (NET) transporters are molecular targets for different classes of psychotropic drugs. DAT, SERT and NET regulate monoamine concentrations at neuronal synapses by carrying monoamines across neuronal membranes into presynaptic nerve cells, using an inwardly directed sodium gradient as an energy source. Structural information about DAT, SERT and NET transporters and their drug interactions is important for understanding their molecular mechanisms of action, and provide useful tools for new drug discovery. Cocaine and SSRIs share similar molecular mechanisms of action, although cocaine is a highly addictive drug and SSRIs are therapeutic drugs prescribed for the treatment of depression. We have used the crystal structure of Aquifex aeolicus LeuTAa [1] as a template for molecular modelling of DAT, SERT and NET. Psychostimulants and antidepressants have been docked into the DAT, SERT, and NET models to reveal molecular explanations for the various selectivities of these drugs.

Acknowledgements

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L-3

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Virtual Screening Approach as a Potent Technology in Drug Design Campaigns. Methods, Applications and Computational Perspectives.

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In recent years the Virtual Screening (VS) has become increasingly popular, as a alternative approach to HTS in the pharmaceutical and academic researches, especially in hit discovery and lead optimization [1,2].
VS is a technology using high-performance computing to analyze large database of chemical compounds to identify possible drug candidates (top-ranked hits) for biological evaluation [3]. Virtual screening methods could be divided into structure-based and those using active compounds as templates (ligand-based VS). The type of methods used in VS are strongly dependent on information available as an input. Hence, a lot of different approaches to VS are known, combining one or more methods in one protocol. A broad range of computational techniques (e.g. 2D fingerprints, 1D molecular descriptors, docking and scoring, pharmacophore similarity search, clustering), machine learning (e.g. ANN, RF, SVM, NBC, SOM, BKD, etc.) and statistical (e.g. PCA, DPD, ROC) methods can be applied [4].
Here, we show our implementation of multistep approach to virtual screening (mVS) of commercially available compound libraries. The databases of the largest vendors such as Enamine, ChemBridge and ChemDiv have been analyzed, adopted and used as a molecular screening space (approx. 3M compounds). Some examples are provided to further demonstrate the effectiveness of this technology in hit discovery [5].
In order to increase the overall efficiency, the mVS is still extensively expanded and great efforts are being made to develop and validate new tools, methodology and infrastructure.

Acknowledgements
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L-4

High Throughput Calcium Screens for Identification of Potential Drugs for Alzheimer's Disease.

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Calcium signaling regulates multiple neuronal functions including synaptic transmission, plasticity and cell survival. Dysregulation of calcium homeostasis undergoes subtle changes during physiological ageing and affects neuronal function and survival. Neurodegenerative diseases related to aging, such as Alzheimer's disease, Parkinson's disease or Huntington's disease, are characterized by calcium buffering impairment, alterations in calcium entry routes into neurons, as well as by mitochondrial and endoplasmic reticulum dysfunctions.

No effective treatments are available for those diseases. To identify potential drug targets allowing restoring calcium homeostasis the high throughput screens (HTS) are needed. The available techniques of calcium measurements using for instance calcium probe FURA-2 cannot be used for HTS. In collaboration with Dr. Jochen Herms's group in Munich we are analyzing the suitability of several protein calcium sensors for such screens. The probes are stably or transiently expressed in cells with mutated presenilin 1 responsible for early onset of Alzheimer disease (FAD). We found using OPERA system that it was possible to analyze in HTS format changes of calcium concentration in cells expressing CASE12. The OPERA from Perkin-Elmer (Evotec technologies) is a fully automated system allowing confocal imaging of cells cultured in microtiter plates. Due to automated image acquisition, data processing, cell recognition and signal discrimination in cells cultured in 384 microtiter plates, the effect of several hundreds of compounds on cultured cells can be analysed within a few hours. We screened about 20 000 substances looking for compounds that will affect cellular calcium concentration in cells with impaired calcium homeostasis due to presenilin mutations. In parallel, we try to develop another HTS based on changes in protein-protein interaction occurring as a result of depletion of calcium ions from endoplasmic reticulum. This method should allow HTS in samples from genetically unmodified cells such as human lymphocytes. The data from both types of screens will help to identify potential drug targets within calcium signaling components and lead structures affecting these targets.

L-5

Intracellular Signaling in Alzheimer Disease.

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Alzheimer's disease (AD) is a progressive and degenerative brain disorder that has emerged as one of the major public health problems in adults. AD is characterized by the hippocampal deposition of fibrils formed by amyloid b-protein (Ab), a 40- to 42-amino-acid peptide. The folding of Ab into neurotoxic oligomeric, protofibrillar, and fibrillar assemblies is believed to mediate the key pathologic event in AD. Recent studies suggest that Ab specifically interferes with several major signaling pathways in neuronal cells: canonical MAPKinase cascades (ERK, p38), Wnt and Notch signaling, or JAK/STAT axis. Ab acts at memory-forming pathways located downstream of the glutamate ionotropic NMDA and metabotropic mGluRs receptors, affecting signaling proteins ncluding the Ca-dependent protein phosphatase calcineurin, Ca/calmodulin-dependent protein kinase II (CaMKII), protein phosphatase 1, and cAMP response element–binding protein (CREB). Potential involvement of these pathways in in Alzheimer disease pathology is discussed.
Additionally, new strategies of therapeutic interventions targeting AD at the molecular level , including the use of histone deacetylase inhibitors are briefly discussed.

L-6

Role of LEF1/beta-Catenin Complex in Regulation of Gene Transcription in the Adult Brain.

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β-Catenin is a downstream target of lithium, which is an efficient mood stabilizer and the golden standard in the treatment of bipolar disorder. Yet, the role of activated nuclear β-catenin in the adult brain remains elusive. We have found that in the adult brain nuclear β-catenin accumulates in neurons of the thalamus, where it can regulate gene expression. In the lecture, our *in silico* analysis and experimental data will be presented, identifying new β-catenin gene targets in mature thalamic neurons. Then, we will focus on one of the targets, *Cacna1g* encoding the Cav3.1 T-type calcium channel subunit, which contributes to electric signal propagation in the thalamus. We will present *in vitro* and *in vivo* evidence confirming the hypothesis that β-catenin, together with LEF1/TCF transcription factors, activates expression of *Cacna1g* and enhances T-type calcium current. The possible implications (hypothetical) for understanding of the mood disorders pathogenesis will be discussed.

L-7

The Future of Antibiotics.

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Since the discovery of penicillin, pharmaceutical companies have indroduced more than 100 antibiotics to combat a variety of bacterial infections. Clinical application of these antibiotics in the last 50 years almost eradicated major infectious diseases, thus decreased mortality and morbibity, especially in the industrialized countries. The chemical modification of clinically used antibiotics afforded to obtain a number of semisynthetic derivatives with improved activity, greater potency and stability. However, during the last thirty yers only a few novel antibiotcs have been introduced on the global market. The extensive use and misuse of known antibiotics has lead to the selection of microorganisms that either carried mutations or acqiured new genes producing new antibiotics-resistant strains, that have been isolated from patients throughout the world. Emergence of bacterial resistance to a number of antimicrobial agents becoming a major health problem. Moreover, new patogens such as *Legionella pneumophila*, *Campylobacter jejuni*, *Bartonella henselae* or *Borrelia burgdorferi* may also be regarded as a new threat. Therefore, more than 15 million people die every year due to infectious diseases. There is an urgent need to develop a new agents/antibiotics to treat patients infected with drug resistant bacteria. In this lecture a number of research directions in antimicrobial discovery will be addressed to overcome the problem of emergence of multidrug resistant bacteria. Novel antimicrobial targets, novel compounds and novel analogues, multidrug resistance problem, including the bacterial efflux phenomenon will be presented. Application of bacteriophages and their products as an alternative metod in the management of infectious diseases therapy will be also included.

L-8

Multitarget Medicines. Opioid-Tachykinin Chimeric Peptides.

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Our group proposed to develop new chimeric analgesics in which opioid pharmacophores are covalently hybridized with other types of pharmacophores that positively modulate effects of the opioid part. Synergistic enhancement of opioid analgesia and/or decrease of unwanted side-effects should result from such hybridization..

It is generally accepted, that opioids and tachykinins are classified as functional antagonists. However, their spectrum of interactions is much more complicated. Series of new opioid agonist-tachykinin antagonists and opioid agonist-tachykinin agonist conjugates have been synthesized and tested. Hybridization of opioids with tachykinin receptor ligands resulted with new properties that are dependent on their agonist or antagonist nature. In general, hybridization of opioid agonists with tachykinin antagonists resulted in strong analgesia evidencing synergistic interaction between opioids and tachykinin elements. In contrary, the tachykinin agonists may partially reduce opioid analgesic potency of chimeric compounds, but its presence strongly reduces side effects of opioids. In conclusions, both types of hybridized opioid-tachykinin ligands are interesting but with different prospective clinical applications.

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L-9

Chiral Auxilaries in the Synthesis of β-Aminoalcohols.

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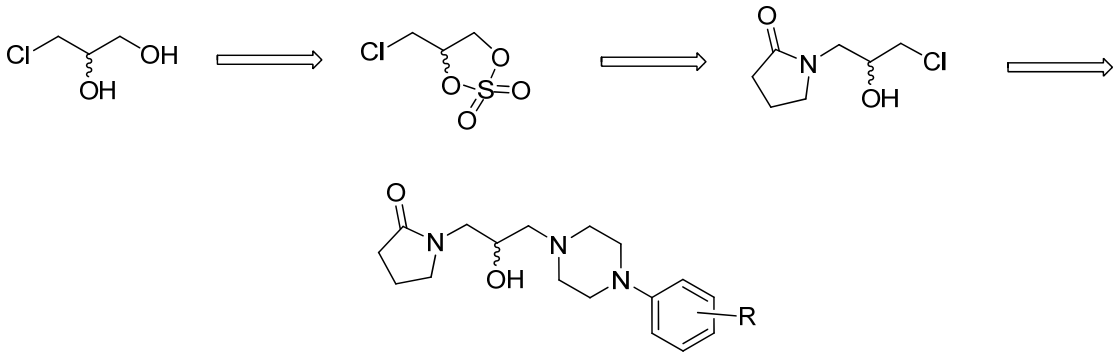
The aminoalcohols comprise a group of compounds that are abundant among the series of □-blockers and other cardiovascular drugs. Each of these compounds possesses at least one chiral centre residing in the alkyl side chain, directly attached to a hydroxy group, and is characterized by inherent degree of enantioselectivity in the binding to the receptor site [1].
There are various methods known for synthesis of this group of compounds involving for example resolution of racemates, enzymatic hydrolysis of acetates or epoxidation of allylic alcohols. All these reported methods suffer from drawback such as the use of expensive enzymes or resolving agents, greater number of steps, low yields or low optical purity. Thus, the problem of synthesizing aminoalcohols as enantiopure or enriched with one enantiomer is still urgent [2].
In the search for new antiarrhythmic and hypotensive agents a series of 1-[2-hydroxy-3-(4-aryl-piperazin-1-yl)-propyl]-pyrrolidin-2-one was synthesised and tested for both *in vivo* and *in vitro* activity.
Initially, our synthetic strategy was based on the epoxide methodology [3], but its drawback connected with ambiguous reactivity of 2,3-epoxypropanes with nucleophiles was the reason for the looking for alternative solution. Based on literature survey it was found that the same fortunate properties as epoxides are shared by another class of vicinally substituted electrophiles – the 1,2-cyclic sulfates [4] and this method was used for the synthesis of compounds design.



R= H, 2-OEt, 2-Cl

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L-10

In Search of New Therapeutics: From Basic Research to the Market Products.

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The studies conducted by the research group of Prof. Jerzy Gębicki are focused on identification of the reactive intermediates (radicals, radical-ions, strained molecules). Both the time-resolved and cryogenic steady-state techniques are used. In recent years a particular attention was paid to the mechanism of multi-step conversion of NADH-NAD^+ with a sequential electron-proton-electron transfer. It was observed for the first time that the radical-cation generated from NADH exists in the enol-form, which is thermodynamically more stable than the keto-form. Both tautomeric forms of NADH radical-cation were spectroscopically characterized and their reactivities were also studied. These studies were summarized in a review [1].
Mechanistic studies on NADH-NAD^+ conversion initiated an interest focused on therapeutic potential of these molecules. Indeed, the therapeutic potential was confirmed for both the reduced (NADH) and oxidized (NAD^+) forms of the coenzyme in various dermatologic diseases and disorders [2-3].
Poor thermal stability of NADH and NAD^+ limits a use of these compounds as active ingredients in dermatologic preparations. Therefore a special attention was paid to the synthetic analogs of these molecules, in particular to NAD^+ analogs, which are thermally stable. Therapeutic properties were studied for many pyridinium salts being synthetic analogs of NAD^+. Among the studied salts particularly interesting therapeutic properties were observed for 1-methyl-3-nitropyridine (MNP^+) and 1-methylnicotiamide (MNA^+). MNP^+ carries interesting cytotoxic properties [4-5], whereas MNA^+ manifests anti-inflammatory, thrombolytic and lipid profile correcting activities [6-8].
The lecture will review the therapeutic properties of MNA^+ observed in the animal model studies as well as in the clinical trails. The application of MNA^+ in medical cosmetics present already on the market will also be discussed.
The lecture will end up with presentation of interesting therapeutic properties of 1-methylpyridine (1-MP^+) and 1,4-dimethylpyridine (1,4-DMP^+), which are formed from trigonelline in a process of coffee roasting and can be regarded as molecules potentially responsible for beneficial effects of coffee drinking.

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L-11

Mining Databases for The Exploration of The Architecture of Drugs.

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Although drugs get better and better, the practical impact of drug design, e.g., QSAR or related methods in pharmaceutical research are still below expectations. In recent years chemistry has seen an explosion of molecular information resources available, e.g., more than 50 million compounds were synthesized and catalogued. Moreover, *in silico* molecular simulations, an increasingly important component of current medicinal chemistry, further contributes to this. A number of molecular databases are publicly available and can be used in drug design, e.g. PubChem and ZINC databases contain ca. 37 and 8 mln compounds, respectively. The efficient analysis of the factual chemical space described in these databases can play an important role in improving current drug design technologies. The so-called *knowledge discovery* approaches allows today not only for the analysis of the simple problems but for the better understanding of the complex molecular architectures, e.g., this of chemistry [1]. In this context, a number of new concepts appeared recently to analyze and describe drug architecture, e.g., druglikeness, ADMET, privileged structures, polypharmacology, etc [2]. We will briefly discuss this and analyze a place of drugs within the *architecture of chemistry*.

We have developed a novel and unique molecular and structural database managing system, MoStBioDat [3], available as a public domain package [4] for the analysis of large ligand libraries. MoStBioDat is not only the dual purpose storage/extraction database platform maintaining the high-standards of data integrity and reliability, but consistent environment providing software-based solutions for the massive *in silico* protocols parallely analyzing small molecule ligand and protein data. Several example of the application of this software will be presented and discussed.

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L-12

Multidirectional Activity Analysis for Some 5-HT_{1A} Receptor Arylpiperazine Ligands.

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Despite confirmed potential of agonists and antagonists of the 5-HT_{1A} receptor in clinical therapy of many health problems, especially of the cns, buspiron – arylpiperazine derivative with pyrimidine moiety was the only one for long time accepted for selling over the banch in the US. Unfortunatlly its market potential was weakened by multiple side effects, like short half-life time or unwanted side-effects of its metabolite – highly active antagonist of the α2 adrenergic receptor. Search for the new, more effective antipsychotic drugs, with less side effects led to development of huge, counting for thousands, population of compounds active towards 5-HT_{1A} receptor. The most important and numerous group of these ligands are intensly investigated arylpiperazines containg long three or four carbon aliphatic linker. Within newly synthesized structural analogues, the buspirone derivatives with pyrimidine moiety very often did not exhibit activity to 5-HT_{1A} receptor or were omitted in synthesis.
For our research 12 azatricycloundecane derivatives [1] were chosen. This group contained compounds both with nanomolar scale activity as well as almost non-active toward 5-HT_{1A} receptor. Moreover pyrimidinyl substituent containing compounds were found in the second group. If, simplifying the problem, one can state that activity is a function of substituent, in our case aryl substituent on the piperazine nitrogen atom, the key task would be finding the cause of the lack of activity for some derivatives investigated, also the buspirone analogues.
For that purpose multidirectional analysis of the group investigated was performed. They included both experimental methods and calculation techniques. They resulted with mathematical, quantitative models of the structure-biological activity relationship toward 5-HT_{1A} receptor and elucidation of the key for activity molecular descriptors. They allowed also selection of the most representative ligands conformations, probably the most numerous in the physiological environment.
The experiments, including calculation of the lipophilicity parameters by ion-pair chromatography and its correlation with molecular descriptors and theoretical lipophilicity, calculated *in silico* with use of multiple, free-available calculation tools, allowed explanation of the performed retention process as well as confirmation of the previous SAR of the 12 selected azatricycloundecanes conclusions.
The datailed investigation of potential molecular mechanism of interaction of the 5-HT_{1A} receptor and selected compounds was also performed. It confirmed that not the requirements of the receptor binding pocket but basisity/acidity of the ligands determine their activity.

Computations were performed in the framework of computational grant by Interdisciplinary Centre for Mathematical and Computational Modelling, Warsaw, Poland, grant number G30-18.

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PREZENTACJE USTNE
KOMUNIKATY

K-1

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Ligand Interactions and Ligand-Induced Conformational States of the Serotonin Transporter.

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The serotonin (5-HT) transporter (SERT) is the main molecular target for the selective serotonin reuptake inhibitors (SSRIs), currently the most prescribed antidepressant drugs. As the three dimensional (3D) structure of SERT is unknown, the prokaryotic homologous leucine transporter (LeuT) crystal structure of *Aquifex aeolicus* was used as a template to generate a homology model of SERT. Docking of substrates (tryptamine derivatives) and one inhibitor (S-citalopram) into the putative substrate binding site showed that the ligands may bind in two putative binding modes. In both binding modes, the protonated amine of the tryptamine derivatives was located near the D98 carboxyl side chain forming an ionic interaction, which is in accordance with experimental data. The two binding modes of the tryptamine derivatives differed in the orientation of the indole ring nitrogen and the orientation of the 5-position. In the most realistic binding mode of S-citalopram all sub-pockets of the putative substrate binding site were occupied. The amine moiety of the ligand was contained in the ionic sub-pocket, whereas the cyanophtalane and fluorophenyl moieties were located in the hydrophobic and aromatic sub-pockets, respectively. This binding mode is very similar to the binding mode suggested from mutational mapping of S-citalopram. Two 5-HT- and two S-citalopram-SERT complexes, as well as SERT alone, were embedded in a POPC lipid bilayer and >20 ns of molecular dynamics simulations were performed. The simulations indicated that substrate transport by SERT may involve the formation and breakage of ionic interactions and the winding and unwinding of α-helical structure.

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K-2

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Comparison of Ligand Docking to Different SERT Conformations.

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The serotonin transporter (SERT) plays a key role in the regulation of synaptic serotonin (5-hydroxtryptamine, 5-HT) levels and therefore is the major target for antidepressants including both the tricyclic antidepressants and selective serotonin reuptake inhibitors. The antidepressants affect the concentration of the serotonin by inhibiting the reuptake of the 5-HT into pre-synaptic nerve cells.
To examine the molecular mechanism of SERT, the interactions between SERT and ligands with different binding affinities were studied. Two different models representing different conformational states of SERT were used. One model represented the substrate-occluded conformation closed at both sides, while the other model represents an outward-facing conformation. X-ray crystallographic structures of corresponding conformational states of the bacterial homologue of the Na^+/Cl^- dependent neurotransmitter transporters from *Aquifex aeolicus* ($LeuT_{Aa}$) [1, 2] were used as templates for the homology modelling. The ligands were docked into the binding site of both models using the automatic docking module of the ICM molecular modelling software. Asp98 in TMH1 was the anchoring point for ligand docking into SERT models. In both models the docking studies indicated that the ligands interacted strongly with amino acids in transmembrane helix 1, 3, 6 and 8 of SERT. In the model of the outward-facing conformation the ligand also interacted with aminoacids in the extracellular loop 4 (EL4).

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K-3

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The Implementation of an Expert System to Search for Novel Substances Acting on Serotonergic and Glutamatergic Systems.

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As part of an academia-based platform [1] to discover substances acting on serotonergic or glutamatergic systems as potential new antidepressant or anxiolytic drugs, an expert system recognizing potential activity of new compounds was developed. Both receptor systems are among the most diversified, so we focus our attention only on targets implicated in depression and anxiety, i.e.: serotonin transporters (SERT), 5-HT_{1A}, 5-HT_6 and 5-HT_7 receptors and metabotropic glutamate (mGlu) receptors of group II (mGluR2, 3) and III (mGluR4, 7, 8).
The expert system [2] uses Bayes classification [3] as a methodology, MOLPRINT 2D fingerprints as structure representation and is run under Canvas [4]. In general, the system is based on databases of known ligands for the above targets, and is trained in supervised learning setting on correlations between fingerprints and activities. Bayes classification is a simple probabilistic classifier which assumes that presence of some feature is independent on the presence of another. It is especially useful for classification of arguments described by multidimensional variables (like fingerprints [5]). As a result the system indicates compounds potential activity as boolean value. For example, the 5-HT_7 module (based on 470 known ligands) shows 72,7% and 98,6% efficacy in recognizing active and inactive compounds from internal test sets.

The study was partly supported by a grant PNRF-103-AI-1/07 from Norway through the Norwegian Financial Mechanism

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[5] Sastry M., Lowrie J. F., Dixon S. L., Sherman W.: *J. Chem. Inf. Model*. 50 (2010), 771.

K-4

Fluorescent probes – types and applications.

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Fluorescence is a methodology used extensively by scientist representing many different disciplines. It is also commonly applied in flow cytometry, medical diagnostics, DNA sequencing and genetic analysis – just to give a few examples. Fluorescence-based detection is nowadays the most common because of its high sensitivity, simplicity, and diversity. Recent advances in fluorescence probes development, new specific labelling strategies, and improved spectroscopic instrumentation are responsible for the major breakthrough in cellular imaging, single molecule detection and the biomolecular research.

Fluorescent probes represent the most important part of fluorescence spectroscopy: spectral properties of fluorophores determine both the excitation and emission wavelengths, time resolution and instrumentation used during the experiment. Fluorophores can by generally divided into two main classes – intrinsic and extrinsic. Intrinsic fluorophores are these that occur naturally in nature such us aromatic amino acids, NADH, flavins or chlorophyll. Extrinsic fluorophores are added to the sample to provide a specific fluorescence. There is a wide variety of extrinsic probes characterised by different spectral properties, reactivity and environmental-sensitivity, able to covalently or noncovalently bind to proteins, lipids and nucleic acids. Among them are the small organic fluorophores represented by the Dansyl, fluoresceine, rhodamine or cyanine dyes and green fluorescent proteins as well as inorganic fluorophores such as semiconductor nanocrystals (quantum dots), lanthanides and transition metal-ligand complexes.

It seems that the newly introduced labels i.e. metal nanoparticles, quantum dots or green fluorescent proteins are starting to replace traditional organic dyes because of their superior optical properties, such as brighter fluorescence, wider selections of excitation and emission wavelengths and higher photostability. However, there are still disciplines such as biomembrane science or physical biochemistry were the traditional organic fluorescent probes are irreplaceable because of their size, environmental-sensitivity and selectivity.

The presentation will summarize recent advances in fluorescence probes applications and development.

K-5

Glycosylation of Peptides.

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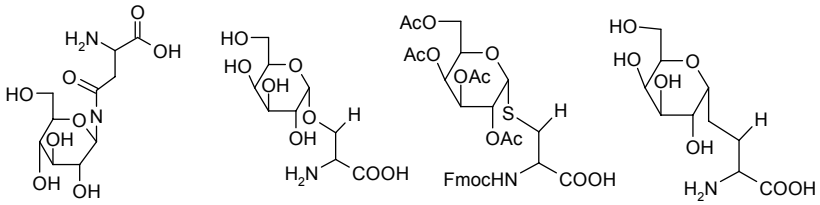
An important process of posttranslational modification of proteins involves attachment of appropriate residues with covalent bond to one or several side chain functional groups [1]. This process of modification of structure is common in Nature and leads to differentiation of properties and functions of proteins. One of the most important pathways involves carbohydrates used to glycosylation of peptides and proteins [2]. Four groups of glycosylated proteins (peptides) are known: N-glycans with carbohydrate residue attached with asparagine (Asn), O-glycans with carbohysrate moiety attached to hydroxyl group of serine or threonine, S-glycans involving SH group of cysteine, and C-glucans formed by attachment of sugar residue to C-atom of other amino acids.



We found that designed in Institute of Organic Chemistry triazine coupling reagents are very useful in the synthesis of *N*- and *O*-glycosylated building blocks as well as in the synthesis of glycopeptides in the classic solution phase synthesis and in solid phase peptide synthesis. Efficiency of triazine reagents were confirmed in the synthesis of the double glycosylated fragment of gp120 292-300 protein, synthetic monoglycosylated epitope CSF114 used as diagnostic for Sclerosis Multiplex (SM), monoglycosylated fragment (30-50) hMOG proteine and fragment FAN(635-655)Glc protein.

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K-6

An Approach for Application of Synthetic Peptides as Markers of Autoimmune Diseases.

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Development of autoimmunologic or atherosclerotic diseases is a multifaceted process depending on genetic and environmental background, but also on chronic bacterial or viral infections. In the latter case one of the most essential factors is the molecular mimicry of human proteins and pathogenic antigens of *P. mirabilis*, *H. pylori*, *Chlamydia* and many others. Recently, several reports were published suggesting an essential role of *H. pylori* infection in pathogenesis of ischemic heart disease, idiopathic thrombocytopenic purpura, iron-deficiency anemia, and atherosclerosis. Taking into account that bacterial ureases have been suggested as dominant antigen detected in infested patients, we selected them as the privileged target in the search for the new markers of coronary heart diseases as well as *Helicobacter*-induced gastritis.
H. pylori, *Proteus sp*, *Vibrio sp*, *Staphylococus*, *C. ensiformis* urease fragments (8-19-mer peptide sequences) were synthesized on the cellulose support and used in the diagnostic tests. In these studies 40 healthy blood donors and 30 atherosclerotic patients were involved. It has been observed significantly stronger reactions of synthetic BK-61A peptide with *H. pylori*-infected atherosclerotic patients than with *H. pylori*-infected healthy blood donors [1]. Analysis of homology by the Basic Local Alignment Search Tool (Blast), shown 75% similarity of amino acid sequences between *H. pylori* urease fragment SIKEDVQF with several human proteins.

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K-7

Studies on Phenylalanine-Based AMPA/KA Receptor Ligands.

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Glutamate- and GABA-releasing neurons form two basic, excitatory and inhibitory systems responsible for neurotransmission in the mammalian central nervous system. Fast excitatory synaptic transmission in the CNS relies almost entirely on the neurotransmitter glutamate and its family of ion ligand-gated channel receptors (iGluRs). The family of iGluRs is divided into three functionally distinct subclasses: NMDA, AMPA and kainate receptors. Structurally, AMPA-receptors are cation-selective tetrameric heterooligomers formed by combinations of the highly homologous subunits GluA-4, while kainate receptors are tetrameric assemblies of GluK1-5 subunits. There is a clear pharmacological boundary between NMDA and other iGluRs, however, most of AMPA agonists and antagonists activate also kainate receptors and only few compounds discriminate between individual subunits.

The present project is focused on the search for new potent and selective competitive AMPA and/or KA receptors ligands. On the basis of published crystal structures of the GluA2 and GluK1 binding cores, series of compounds with the general structure based on the phenylalanine scaffold was designed and synthesized. The influence of the nature and position of substituents in the phenyl ring on the affinity to both native (NMDA, AMPA, KA) and cloned (GluK1, GluK2, GluK3) receptors was studied. Chosen analogs were also examined by TEVC electrophysiology of iGluR expressed in *X. laevis* oocytes. Within the group of obtained amino acids several AMPA-prefering as well as GluK1 and GluK3-prefering compounds were identified, among which ligands acting selectively at GluK1/3 receptors seem to be the most promising.

In an attempt to explain the pharmacological data of the target amino acids, two complexes of the most active phenylalanine analog bound to GluA2 as well as GluK1 binding cores were co-crystallized and solved. Comparison of their binding modes allowed to draw conclusions on the structural determinants influencing affinity and selectivity at non-NMDA ionotropic glutamate receptors within the described group of compounds.

This work was partly supported by Polish Ministry of Science and Higher Education, Grant Nr N N405 303936

K-8

Synthesis and Pharmacological Evaluation of new Sildenafil Analogues.

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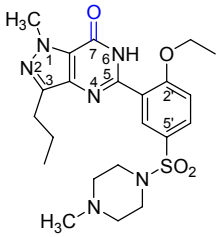
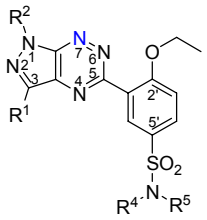
Sildenafil1 (Viagra) is the one of the selective phosphodiesterase 5 (PDE5) inhibitors, and is a widely used oral agent for the treatment of male erectile dysfunction (MED). Despite its effectiveness, sildenafil has shown clinically significant adverse reaction such as nausea, headache, facial flushing, and visual disturbance. It has been postulated that some of these side effects may be ascribed to the modest selectivities toward the other PDE isoforms. Therefore, the search for more potent and selective PDE5 inhibitors with improved selectivities against these PDE isoforms and greater potency for PDE5 inhibition have recently attracted considerable interest.2-7

Herein we report our research on the synthesis and pharmacological evaluation of new sildenafil analogues, in which the C=O group in the pyrazolopyrimidine portion of sildenafil has been replaced by a nitrogen atom.

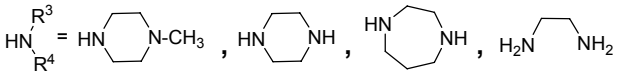


Sildenafil



Sildenafil analogues

R^1 =CH_3, C_3H_7
R^2 = CH_3



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K-9

Urokinaze Inhibitors.

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The urokinase-type plasminogen activator (uPA), a trypsin-like serine protease, plays an important role in several biological processes including tissue remodeling, cell migration and matrix degradation. The primary role of uPA is conversing plasminogen into its active form of plasmin, a broad spectrum serine protease, which participates in the fibrinolytic cascade. u-PA as well as plasmin are strongly associated with tumour cells by influencing tumour initiation, proliferation, migration, invasion, formation metastasis and apoptosis. Both enzymes act directly by proteolysis, and plasmin also indirectly through the activation of matrix metaloproteases. Overexpression of uPA has been found in various malignant tumours, especially in the digestive system, the respiratory system, bones, skin, breast, the genital system, the urinary system, brain and leukemia. High levels of urokinase are correlated with enhanced invasiveness, metastasis and poor prognosis.
The inhibition of plasminogen activation by uPA appears to be an attractive approach to the therapy of tumour growth and metastasis. Studies demonstrated that the S1 pocket of uPA is the critical site of interaction of inhibitors. The P1 positively charged residue of an inhibitor (arginal, benzamidine and phenylguanidine) makes a salt bridge with Asp189 in the S1 pocket of uPA. The residue of P2 is accommodated in S2 side limited by His57 and should be hydrophobic. When the P3 position is occupied by an unnatural D-amino acid, the side-chain projects into the S4 pocket. The S4 site of uPA contains His-99, and the residue of D-Ser could form a favorable interaction with this site.
H-D-Ser-Ala-Arg-H inhibitor reported by Tamura contains unusual but useful D-serine as P3 residue which does not interact with trypsin-like proteinases and it is not hydrolized *in vivo*. However, aldehyde derivatives are alkylating agents and they irreversibly inhibit uPA.
On the basis of this peptide sequence we synthesized a series of tripeptides as potential inhibitors of urokinase. The first series were compounds of the general H(Ac)-D-Ser-Ala(Gly)-Arg-OH(NH_2) formula [1]. The most active inhibitor of urokinase was H-D-Ser-Gly-Arg-OH. The second series of peptide analogs of arginine synthesized in our lab were the amides of peptides H-D-Ser-Ala-Arg-NH-X [2]. H-D-Ser-Ala-Arg-NH-$(CH_2)_5$-NH_2 inhibited urokinase with Ki value of 6.3 μM. The third series of compounds with D-Ser-Ala-Arg sequence were N-sulfonylamides peptides [3]. 2,4,6-triisopropylphenyl-SO_2-D-Ser-Ala-Arg-OH was the most selective inhibitor of urokinase and α-tolyl-SO_2-D-Ser-Ala-Arg-OH was the most active inhibitor of uPA with Ki value 24 μM. The next series were tripeptides with amino acids with aliphatic/aromatic/cyclic side chain as P2 residue [4].
We present effect on the amidolytic activities of urokinase, thrombin, trypsin, plasmin, t-PA and kallikrein of the synthesized compounds. The obtained peptides were tested for their hemolytic activity on pig's erythrocytes and for their in vitro antitumour activity in the following human breast cancer cells: standard MCF-7, estrogen-independent MDA-MB-231 and colorectal adenocarcinoma tumour DLD line.

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PREZENTACJE USTNE
POSTERY

PP-1

The Novel Derivatives of Methylpiperazine and 4-Methylhistamine with Moderate Affinity for H4R.

Monika Szuster [a], *Urszula Kijkowska-Murak* [a], *Dariusz Matosiuk* [a], *Katarzyna Kieć-Kononowicz* [b]

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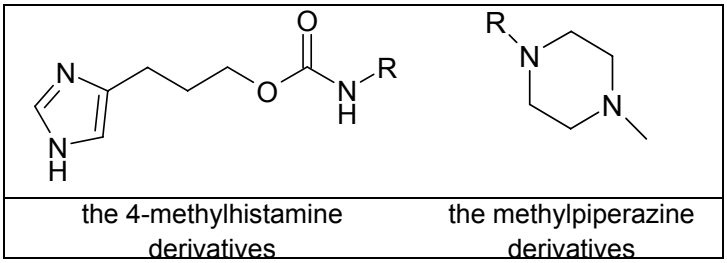
H4R is the novel member of the histamine receptor family. It was cloned by several groups independently in 2000 and 2001. H4R plays a crucial role in allergy and inflammation, therefore, H4 antagonists can become the new antihistamines and may be used against some allergic diseases effectively in the near future. H4R is therefore a promising target for drug design. Until now there is a high interest for JNJ7777120 and its application for *in-vivo* researchs regarding many diseases such as: asthma, pruritus, peritonitis, pleurisy and cancer. In the search for novel H4 antagonists or inverse agonists, a variety of ligand classes have been identified: the novel derivatives of methylpiperazine and 4-methylhistamine.

The aim of presented work was the investigation of molecular interactions of two groups: novel derivatives of methylpiperazine and 4-methylhistamine with moderate affinity for H4R. The investigated groups of H4R ligands are interesting because of their affinity for H4R (values micro- and nanomolars).

The investigation started with the construction of H4R with the aid of the homology modelling with β2 adrenergic receptor (2RH1 used as template in this study). The binding pocket was validated by molecular docking of different agonists and antagonists of H4R, which structures were taken from the Cambridge Structural Database. The 3D-structures of investigated derivatives were generated with the aid of the program Spartan'08. The energy and geometry of all derivatives were optimized by semi-empirical method PM3. The optimisation of geometry and the minimisation of energy was performed for both neutral and protonated molecules The final protonated structures of methylpiperazine and 4-methylhistamine derivatives were docked into H4R model. Interpretation of the docking these derivatives allowed indicate the crucial residues in the binding pocket of H4R and explain the molecular mechanism of the interaction: ligand – H4R.



the 4-methylhistamine derivatives | the methylpiperazine derivatives

PP-2

RP-TLC Determination of the Lipophilicity of N-4-Arylpiperazin-1-yl-propyl Imidazolidine-2,4-dione and Pyrrolidine-2,5-dione.

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Lipophilicity is a fundamental physicochemical property of bioactive compounds that play a pivotal role in the transport of a molecule through cellular membranes and influences the localization of compound in the therapeutic site of action [1].
In aim to evaluate the structure-anticonvulsant activity relationship in a group of imidazolidine-2,4-dione and pyrrolidine-2,5-dione (fig. 1), we estimated their chromatographic R_{M0} parameters, using the reversed – phase thin layer chromatography (RP-TLC) method. The experimental R_{M0} values were compared with the theoretical partition coefficient calculated by a module of the Pallas and Marvin programs [2, 3].

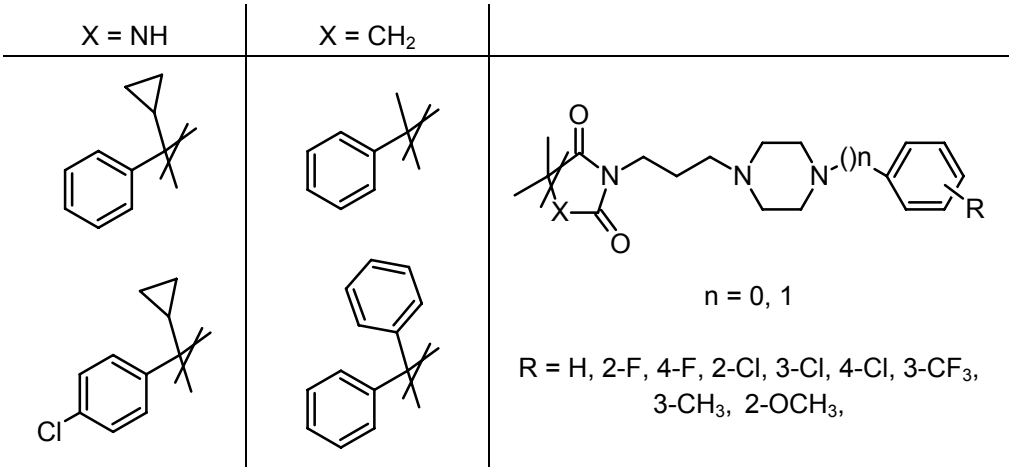

Fig. 1

The tested compounds were evaluated for their anticonvulsant activity through the Antiepileptic Drug Development (ADD) Program developed by the National Institute of Health (Rockville).

This study was supported by the Polish MNiSW grant No. N N405 298536.
Acknowledgements: We thank Dr J. Stables from National Institute of Neurological Disorders and Stroke, Rockville, Maryland, USA for anticonvulsant testing in the frame of ASP.

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PP-3

Chiral and Specific Activity of Immobilized, Recombinant D-Hydantoinase Towards Racemic Phenyl Ring Substituted 5-Benzylhydantoin Derivatives.

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In recent years industrial demand for D-hydantoinases with enhanced activity and substrates specificity have been growing rapidly. Hence, up to now natural habitats of the enzymes involved in hydantoinase method have been intensively screened for the presence of microbes having high levels of D-hydantoinase activity. Moreover, the introduction of D-hydantoinase gene into *Escherichia coli* by employing recombinant DNA techniques and next their expression or co-expression lead to enhanced activity, increased enantioselectivity and enlarged substrate specificity of examined enzyme. Additionally, the immobilization technique offers many advantages including: the easy separation of the latter from the reaction products, the elevation of enzyme concentrations per unit volume, and even the enhancement of enzyme stability and activity [1-4].
In the present work, we report the use of D-hydantoinase, recombinant, immobilized from *E. coli* for the biosynthesis of *N*-carbamoyl derivatives of several ring-monosubstituted and ring-disubstituted D-phenylalanine analogs, which are next easily converted to the corresponding D-amino acids. The required 21 racemic phenyl ring-substituted 5-benzylhydantoins were synthesized using at first Knoevenagel's condensation and then either the catalytic hydrogenation of non-saturated bond in 5 position of the hydantoin ring in the presence of Pd/C catalyst or by reduction of appropriate 5-arylidenehydantoin with 57 % hydroiodic acid in the presence of red phosphorus (5).
To study the activity of D-hydantoinase towards all obtained phenyl ring-substituted 5-benzylhydantoins the calibration curves for each substrate were estimated by capillary electrophoresis. Obtained regression equations were used to calculate the concentrations of substrates remaining at the time in the reaction mixtures. The efficience of the enzyme was expressed in terms of k (reaction rate constant) and $t_{0,5}$ (substrate half-life). Reaction rate constant and substrate half-life in different pH conditions were also estimated. To determine enantiomeric purity of the obtained D-phenylalanine derivatives, enantiomeric ratio (%ee) for each examined compound was calculated using either HPLC or CE technique.

Acknowledgement:
Project co-financed from the European Social Fund and national budget in the frame of The Integrated Regional Operational Programme. Partly supported by Polish Ministry of Health and Higher Education grant: N405 2518 33

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PP-4

Novel Dual Binding Site Cholinesterase Inhibitors with Phthalimide Moiety.

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Alzheimer`s disease (AD) is the most common neurodegenerative brain disorder of the 21st century. AD is characterized by progressive dementia caused by the deficits in the cholinergic system in the brain areas related to memory and learning, brain deposits of amyloid beta (Aβ) peptide and neurofibrillary tangles. The most important drugs for the treatment of Alzheimer`s disease are inhibitors of cholinesterases such as donepezil, rivastigmine and galantamine. Acetylcholinesterase inhibitors (AChEI) can interact at the active, catalytical site of the enzyme as well as at the peripheral anionic binding site (PAS), the latter one considered to have the ability to bind to Aβ peptide thus promoting fibrillogenesis. One of the new strategies in design of anti-AD drugs is the synthesis of compounds, which can interact at both binding sites of cholinesterases. [1,2]
In our previous work, *N*-benzylpiperidinoaminoalkyl derivatives of isoindoline-1,3-dione (phtalimide) were obtained [3]. These compounds showed inhibiting activity against both enzymes (AChE and BuChE), and some of them also displayed β-amyloid antiaggregating effect. As a continuation of this study, using molecular modeling and fragment based methodology, new structures with different aminoalkyl moieties have been designed. Then, new analogues of the active phtalimide derivatives, bearing different aminoalkyl moieties instead of *N*-benzylpiperidine group, were obtained. The activity of synthesized compounds was evaluated *in vitro* using the spectrometric method of Ellman. Among the novel compounds, the *N*-diethylamine derivatives exhibited inhibiting activity against AChE. Their IC_{50} values ranged between 0,9-19,5 μM. The structure of the most potent selective AChE inhibitor is presented in Figure 1.

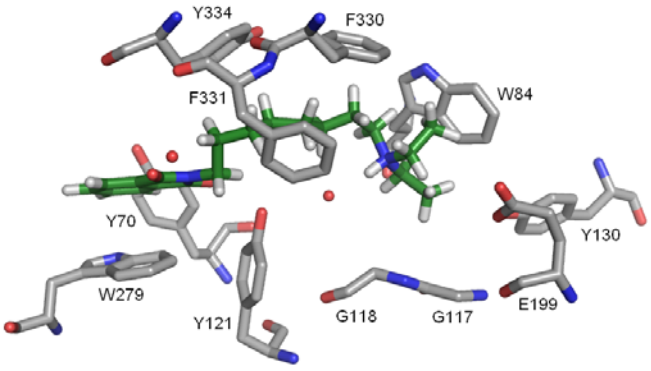

Fig. 1

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PP-5

Synthesis and Anticonvulsant Activity of New *N*-[4-(Arylpiperazin-1-yl)]-(3,3-Dimethyl-2,5-Dioxopyrrolidin-1-yl)- and (3,3-Ethyl-2,5-Dioxopyrrolidin-1-yl)-Acetamides.

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Numerous compounds are synthesized and screened for their anticonvulsant activity each year. To make the discovery of new anticonvulsants more rational many investigators identified structural fragments essential for anticonvulsant properties. One of the structural features that plays a significant role for antiepileptic activity is an amide function [1-2]. In the course of developing new anticonvulsant agents as well as taking into consideration the above and vital influence of 4-arylpiperazine moieties on anticonvulsant activity of pyrrolidine-2,5-diones differently substituted at 3-positon of succinimide ring [3,4], in the present studies we have synthesized a library of (3,3-dimethyl-2,5-dioxopyrrolidin-1-yl)- and - (3,3-ethyl-2,5-dioxopyrrolidin-1-yl)- acetamides with differently substituted piperazines as an amide function. The structures of compounds obtained are shown on **Figure 1**.

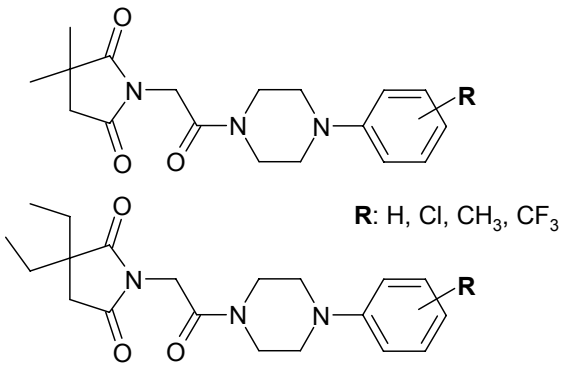

Figure 1.

The desired compounds were prepared by condensation of (3,3-dimethyl-2,5-dioxopyrrolidin-1-yl)- and (3,3-ethyl-2,5-dioxopyrrolidin-1-yl)-acetic acids with the appropriately substituted piperazines, in the presence of the *N,N*-carbonyldiimidazole (CDI) reagent.
The compounds were evaluated for their anticonvulsant activity and neurotoxic properties within the Antiepileptic Drug Development (ADD) Program (Epilepsy Branch, Neurological Disorders Program, National Institute of the Neurological and Communicative Disorders and Stroke (NINCDS), Rockville, USA) [5].

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PP-6

Photochemical Properties of Novel Porphyrazines and Phthalocyanines Possessing Peripheral Fluorine Substituents as Potential Photosensitizers in Photodynamic Therapy.

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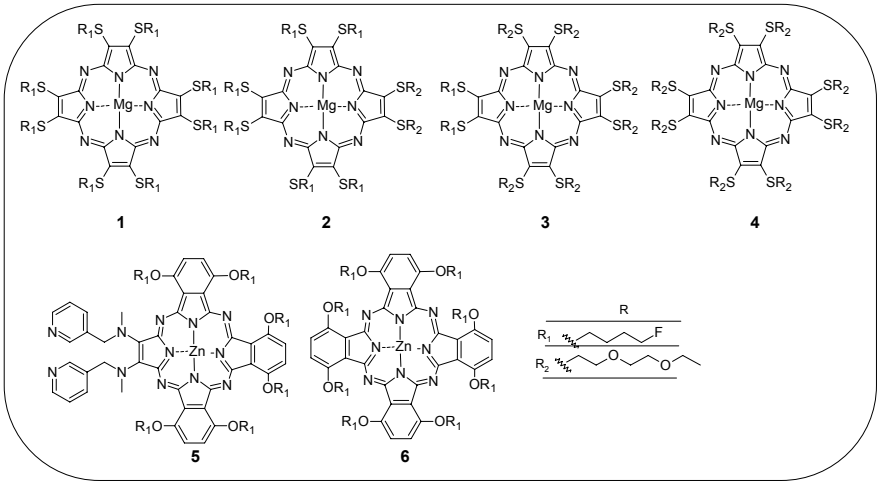
The photosensitizing activity provides an opportunity to employ porphyrazines and phthalocyanines as active agents for photodynamic therapy in medicine. Unsubstituted or metal-free analogues are almost insoluble in water. New derivatives containing appropriate functional groups in the periphery such as amide, carboxylic or sulfonic were obtained in order to overcome solubility limitations. On the other hand, the low solubility of most phthalocyanines in water can be bypassed by the use of liposomes, emulsions or nanoparticle carriers. The aim of our study was to investigate the solvatochromic properties of novel alkylthiol-derived porphyrazines (**1-4**) and alkyloxy-derived phthalocyanines (**5**, **6**).



Solvatochromic effects of macrocycles **1-6** dissolved in the range of protic and aprotic solvents were evaluated by monitoring the changes in the UV-vis spectra. The correlation between the Q band shift towards longer wavelengths and the refractive index of the solvent was tested to assess the solvatochromic effects. The wavelength corresponding to the maximum of the Q band (λ_{max}) was plotted against the rational function $(n^2-1)/(2n^2+1)$ of the solvent refractive index n following the procedure [1,2]. The most significant changes in the Q-band were observed for phthalocyanine **6**. The effects of solvation and coordination within the group of macrocycles **1-6** will be presented.

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This study was supported by SBN grant from the University of Medical Sciences in Poznań, 502-05-03313427-50530.

PP-7

Novel Phosphonic and Phosphinic Acid Derivatives as Inhibitors of Bacterial Ureases.

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[b] *Department of Chemistry, Laboratory of Organic Chemistry, University of Athens, Panepistimiopolis, 157 84 Athens, Greece*
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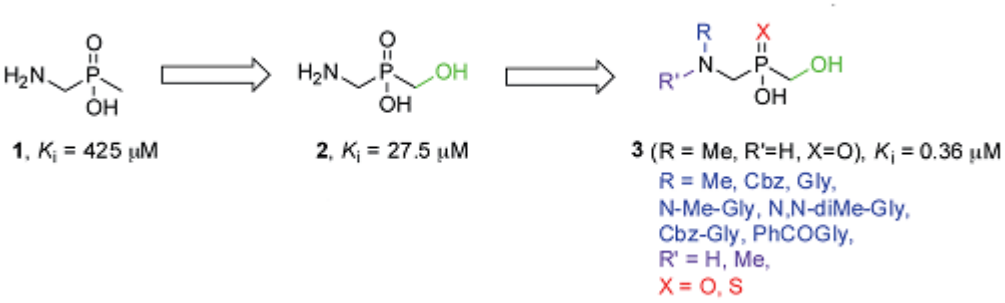

Bacterial urease [E.C. 3.5.1.5] is a nickel-dependent amidohydrolase which catalyses urea decomposition into ammonia and carbon dioxide with carbamate as the intermediate. Infection with ureolytic bacteria causes local rise in pH in areas physiologically neutral or acidic with numerous damaging consequences depending on the colonization site **[1,2].** Therefore effective urease inhibitors consider to be a promising tool for therapy of the diseases caused by urea hydrolyzing microorganisms. Among many active structures previously described (urea analogues, thiols, quinones, and heavy metal ions), inhibitors derived from hydroxamic acid and phosphoramide are the best characterized **[3,4].** In our research we have been elaborating the structure of aminophosphinates as potential inhibitors of bacterial ureases **[5].** Computer aided optimisation of aminophosphinates structure by modification of both N- and P-termini led to invention of novel group of bacterial ureases inhibitors. Introduction of P-hydroxymethyl group resulted in significant increase of inhibitory activity against enzymes isolated from *Bacillus pasteurii* and *Proteus vulgaris*. Designed compounds represent competitive reversible class of urease inhibitors.

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PP-8

Application of Structural Interaction Fingerprints (SIFt) in Identification and Analysis of GPCR Binding-Sites.

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Since high-throughput computational analyzes has become vital aspect of receptor focused studies, as well as ligand research, tools aiding such tasks are strongly desirable. Yet, targets of unknown binding sites are even more challenging computational objectives. Thus, a mean of numerically analyzing docking data becomes extremely helpful while facing such difficulties.
Structural Interaction Fingerprints (SIFt) describe protein-ligand interactions in a simplified binary manner. SIFts employed in our modelling agenda form a nine-digit pattern for each amino-acid in the receptor. This binary pattern portrays interaction as follows:
any | backbone | side-chain | polar | hydrophobic | H-bond acceptor | H-bond donor | aromatic | charged.
Calculations focused on receptor or ligand population give information concerning an average position of ligand groups in each receptor or particular ligand among alternative receptor models.
Averaged, real number SIFt elegantly depicts overall preferences towards particular interactions, enabling construction of a compact scheme of crucial interactions which then facilitate design of a binding mode hypothesis and description of preferred ligand positions within the active site.
Knowledge about metabotropic glutamate receptors' allosteric binding sites (their structural features in particular) is still incomplete. Transmembrane helices boundaries, binding site composition and architecture have not been definitely determined since only indirect data is available. Processed SIFts data yield information about potential binding site, preferred binding mode and facilitate rapid exclusion of incoherent docking results, and so becoming a tool-of-choice for tackling such demanding targets as metabotropic glutamate receptors.

Acknowledgements
This study was partly supported by a grant PNRF-103-AI-1/07 from Norway through the Norwegian Financial Mechanism.

PP-9

Biological Activity of New Derivatives of Dextromethorphan as Potent Allosteric Inhibitors of Neuronal Nicotinic Receptors α3β4.

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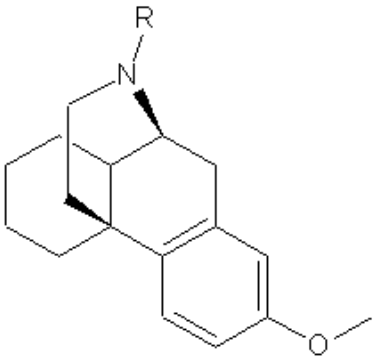
Dextromethorphan (DM) is well known antitussive over-the-counter medicaments but its precise mechanism of action is not completely understood. DM is structurally similar to levorphanol, codeine, and morphine, but in opposite to them has low affinity for opioid receptors. Its complex pharmacology led scientists to suggest several other potential uses (e.g., for a treatment for Huntington's and Parkinson's diseases, stroke and ischemia, seizure disorders, and cocaine dependence). Very interesting is activity of DM as allosteric inhibitor of neuronal nicotinic receptors - particularly α3β4 subtype. This nicotinic receptor subtype is involved in regulation of dopaminergic pathways in brain sections responsible for addiction development. Extensive molecular modeling studies performed in our laboratory allowed identification of binding site within the ion channel and *in silico* design of N-substituted derivatives of dextromethorphan. Some of these new designs were synthesized and characterized structurally [Fig.1].



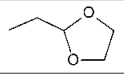
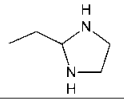
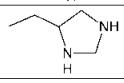
Substance	R–
Dextromethorphan	– CH_3
ZT-01	– $CH_2CH_2CH_2OH$
ZT-02	– CH_2CH_2OH
ZT-03	– CH_2COCH_3
ZT-05	– CH_2CONH_2
ZT-06	– CH_2CN
ZT-07	– CH_2CH_2CN
ZT-09	
ZT-11	
ZT-12	

Fig. 1 The structure of dextromethorphan and selected synthesized derivatives.

In current research these compounds are tested for functional activity against α3β4 nAChR in electrophysiological assay. The *in vitro* experiments are performed on HEK-293 cells stably transfected with rat α3 and β4 neuronal nicotinic receptors genes. Ionic currents in *whole-cell* configuration is measured using a fast drug delivery system DynaFlow. The evoked current measurements allows determining sigmoidal drug – response curve and based on such logarithmic graph we can compute such parameters as EC_{50} for an agonist, IC_{50} for DM and its derivatives, Hill coefficient, dissociation constant etc. Moreover, the results let us to known if the DM and its new derivatives could play a pivotal role in developing new more efficient therapy for nicotine addicted. The latest scientific evidence has demonstrated that α3β4 nAChRs are densely expressed in habenular - interpeduncular (Hb – IPN) system in some way regulate the dopaminergic pathway responsible for addiction development. According to this knowledge the new antiaddictive strategy should be aim to develop new selective allosteric inhibitors of α3β4 neuronal nicotinic receptors.

PP-10

New Fused and Dimeric Azahetarens with Potential Cytostatic Activity.

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The DNA intercalators are rigid molecules containing 3-4 fused aromatic or heteroaromatic rings. The title compounds were synthesized by a few-step synthesis (examples are given in **Scheme 1**). The *PASS Inet* program was used for the choice of suitable starting materials. The program showed that compounds containing indazole, naphthalene, quinoline, pyrazolidone, carbazole, and pyrazole moieties would possess the most promising cytotoxic and antiviral activity. The *vicarious nucleophilic substitution of hydrogen* (**VNS**) (i), using the carboanion precursor **1**, provided products **3**, **7**, **13**, **18** and **23** substituted *ortho* to the nitro group. The nitro group was then reduced (ii) and the resulted amino derivatives **4**, **8**, **14**, and **19** were cyclized by diazotization (iii). The expected pyrazolo derivatives were obtained with good yields under *phase-transfer catalysis* (PTC), or *microwave-assisted organic synthesis* (*MAOS*) conditions. A preliminary biological screening was done for compounds **5** and **9**. Moreover, semi-empirical AM1 and DFT methods were carried out for some of the final products to find the most stable conformation for resulted compounds (examples for **5** and **15** are presented on **Fig. 1**). For final compounds the partition coefficient (*log P*) was calculated using predictions methods – the *ALOGPS*, *ACD Lab/ChemSketch*, and *Pallas* applications.

Scheme 1.

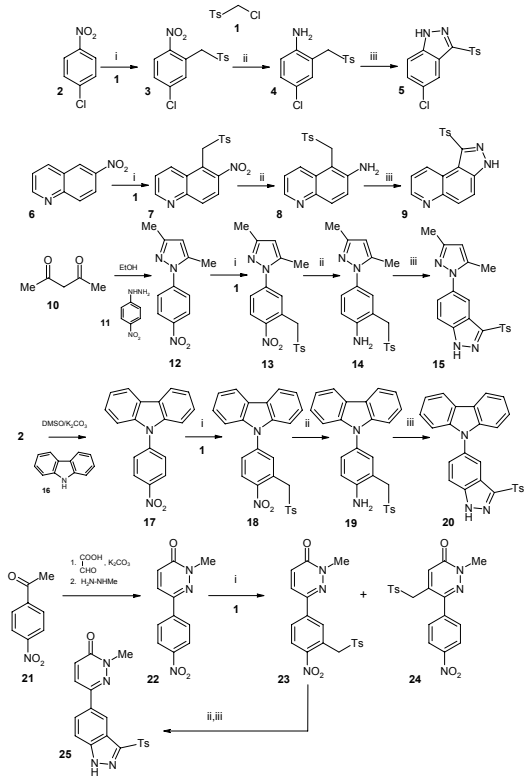
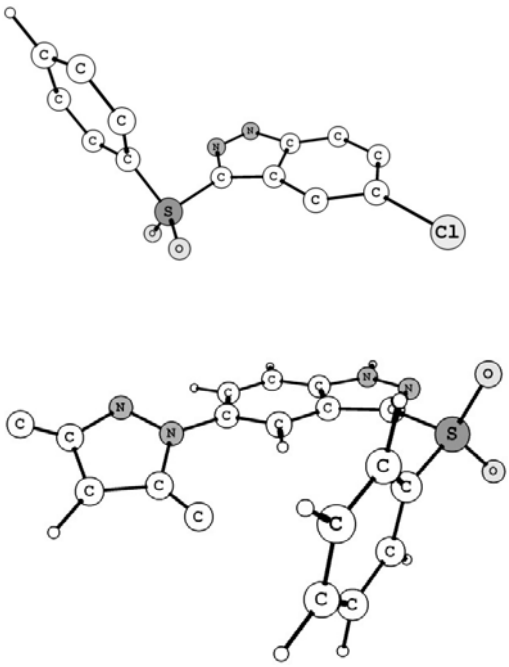


Fig.1.



SBN grant No. 10/2009, and 60/2010 (Poznan University of Medical Sciences)

PP-11

Synthesis of New Imidazofuroxan Derivatives with Potential Biological Activity.

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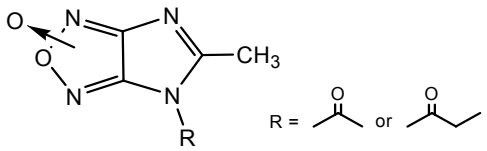
Furoxans (1,2,5-oxadiazole-2-oxides) are important species in various fields of chemistry as synthetic precursors and have found application as high energy materials and biologically active compounds. Furoxan derivatives have recently received particular attention in view of their ability to release nitric oxide, when dissolved in physiological solution in the presence of thiols. Nitric oxide is an important and widespread physiological mediator involved in cellular signaling. It is involved in signals transmission in the cardiovascular, gastrointestinal, genitourinary, respiratory and nervous system[1]. Furoxan derivatives stimulate the guanylate cyclase (sGC) and trigger both antiaggregatory and vasodilating action. Condensed furoxans like benzofuroxans, benzodifuroxans and benzotrifuroxans are systems that have long been known. They have been studied principally for their above mentioned properties. Some of them have been showed also antiviral, antimicrobial, antiparasitic and antitumoral properties[2,3].

In the context of research on the furoxans we have decided to carry of synthesis of some derivatives containing this heterocyclic system. Our earlier works have reported syntheses and showed antifungal and antioxidant activities of many *N*-alkyl derivatives of 4,5-dinitroimidazoles and aminonitroimidazoles[4]. Now we describe usage of these compounds for the synthesis of new imidazole derivatives containing condensed furoxan ring. The furoxan derivatives have been prepared by the oxidation of appropriate *N*-alkyl-*o*-aminonitroimidazoles, bearing at the position *N*-1 of imidazole ring a three or four-carbon aliphatic chain, containing hydroxyl group. The respective aminonitroimidazoles were prepared in the NO_2-substitution reaction of *N*-substituted 4,5-dinitroimidazoles with ammonia. As a result of the oxidation of *o*-aminonitro- derivatives with sodium hypochlorite, two new systems of imidazofuroxan with simultaneous oxidation of hydroxy group in the aliphatic chain in the position *N*-1 of imidazole ring e.g.: *N*-oxide 4-acetonyl-5-methylimidazo[4,5-d]1,2,5-oxadiazole and *N*-oxide 5-methyl-4-(2oxobutyl)-imidazo[4,5-d]1,2,5-oxadiazole were obtained.



Compounds obtained were tested for their biological activity using the *PASS* method (Prediction of Activity Spectra for Substance), which predicts pharmacological effects and biochemical mechanisms on the basis of the structural formula of the compound.

Among researched compounds, all isomers of imidazofuroxans were predicted with high probability (Pa > 0,7). These substances were predicted mainly as vasodilator, antianginal and antiischemic agents. The best results as vasodilator agent were shown for *N*-oxide 4-acetonyl-5-methylimidazo[4,5-d]1,2,5-oxadiazole (Pa = 0,896). These substances may also act as transferase stimulants, platelet aggregation inhibitors or be used in the atherosclerosis and prostate disorders treatment action but with less probability (0,510 < Pa < 0,659).

The imidazofuroxan derivatives, with the estimation of probability of their biological activity, may be researched directly as drugs and also as a scaffold for new active compounds in the future.

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PP-12

Verification of Virtual Screening Results for 5-HT_6 Receptor in *In Vitro* Experiments.

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There are a lot of data indicating pro-cognitive properties and potential therapeutic activity of 5-HT_6 receptor ligands which can be beneficial, among others, in Alzheimer's disease [1], schizophrenia [2] and depression [3].
In the present work we used virtual screening (VS) of an in house (Department of Medicinal Chemistry) library of over 1000 compounds to identify active 5-HT_6 receptor agents.
In silico studies began with the development of homology models of transmembrane domain of 5-HT6 receptor; next, the Support Vector Machine (SVM) method was applied to fingerprint representation of compounds library for preselection of derivatives; and finally 505 agents selected by SVM were docked to the developed homology models. As a result of VS more than 200 compounds with potential 5-HT_6 receptor activity were identified.
The VS results were verified in *in vitro* experiments and K_i values for a selected group of 33 structurally related compounds (in which VS indicated 8 active ligands) were measured.

Acknowledgements:
The study was partly supported by a grant PNRF-103-AI-1/07 from Norway through the Norwegian Financial Mechanism

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PREZENTACJE POSTEROWE

P-1

Synthesis and Antibacterial Activity of New Benzylthiosemicarbazide Derivatives.

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New benzylthiosemicarbazide derivatives were obtained in search for new compounds with potential farmacological activity. 1-Aryl-2-hydrazineimidazoline derived from respective hydroiodides were reacted with benzyl isothicyanate which resulted in 1-(1-arylimidazolidine-2-ylidene)-4-benzylthiosemicarbazide derivatives. Structures of new compounds were described on the basis of elementary and spectral analysis.

Benzylthiosemicarbazide derivatives were screened for their antimicrobial activity *in vitro* against the reference strains of 10 species of aerobic bacteria from American Type Culture Collection (ATCC), routinely used for evaluation of antimicrobials. Microbial suspensions were prepared in sterile saline (0.85% NaCl) with an optical density of McFarland standard 0.5 (150 x 10^6 CFU [Colony Forming Units)/mL]). All stock solutions of the tested compounds were dissolved in dimethyl sulfoxide (DMSO).

Antimicrobial activity of the newly synthesized compounds at concentrations from 31,25 to 1000 □g/mL were screened on the basis of MIC (minimal inhibitory concentration) values by an agar dillution method with Mueller-Hinton II medium.

According to our preliminary results, the tested compounds showed differential activity against Gram-positive bacteria (MIC = 62,5 - 1000 □g/mL). No activity against Gram-negative bacteria was found.

P-2

Synthesis of Benzimidazole, Pyridone and Teophylline Derivatives, and Their Biological Activity.

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Fused dihydrooxazoles were synthesized by the reaction of 2-bromobenzimidazole, 6-bromo-2-pyridone or 8-bromoteophylline with an N-substituted 2,3-epoxypropyl-1-amine. The product derived from 8-bromoteophylline undergoes rearrangement to a dihydrooxazine while other dihydrooxazoles are stable [1, 2]. The obtained compounds were evaluated for their influence on phosphodiesterase activity. For that purpose the PDE Assay Kit was used which is a colorimetric, non-radioactive assay designed in a microplate format. The results showed that investigated compounds inhibit PDE activity in a similar degree as a coffeine standard (10^{-6} M). Inhibition of these isozymes can lead to an increase in cAMP and cGMP levels, which can affect a variety of physiological responses. Selective inhibitors for each of the multiple forms of PDE can offer an opportunity for desired therapeutic intervention and would be an extremely useful tool in drug discovery efforts for a medicinal chemist [3].

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P-3

Oleanolic Acid Morpholide Oximes Acylation as a Method of Synthesis of Highly Effective MDR Inhibitors.

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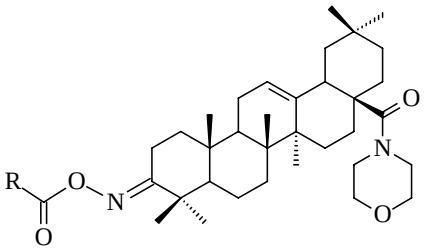
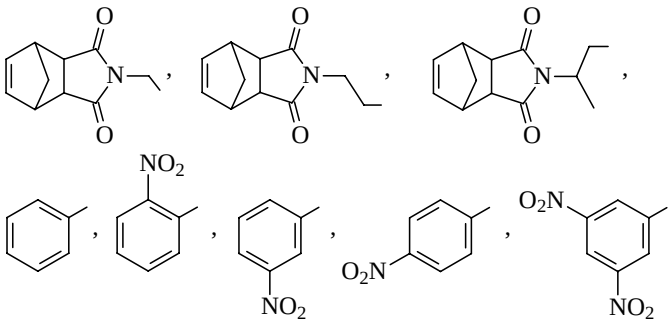
Cancer deseases are still the leading cause of death in the world and they pose the great problem for doctor, because the the index of cancer cure is still not satysfying and cancer treatment is a challenge. The main reason of this situation is the ability of cancer cells for developing varied types of resistance mechanisms, among them the expression of natural or chemically induced multidrug resistance (MDR) and the lack of sensibility for proapoptotic stimulants. Nowadays natural products turn to be one of the most important and promissing source of new substances for cytotoxic drug development and within this group oleanolic acid turns to be the most promissing agent. As it is known from numerous publication, oleanolic acid shows great variety of pharmaceutical activities. The cytotoxic activity of OA against cancer cells [1] as well as hepatoprotective, cardiovascular, immunomodulatory [2] or antiviral [3 – 5] is proved on the basis of biological tests.

R = CH_3–, ICH_2–, $ClCH_2$–, $BrCH_2$–, CH_3CH_2–,



$BrCH_2CH_2$–, $CH_3CH_2CH_2$–,



To obtain new highly active MDR inhibitors, oleanolic acid was subjected to a set of reaction leading to the derivative with hydroxyimine function which was then replaced by the action of carboxylic acid in dioxane. The structures of the obtained compounds were established on the basis of spectral data. Many of the obtained compounds are now tested towards anticancer activity, especially against many tumorous MDR cell lines. Some of them are under research for antiviral and antinociceptive activity which courses of action were predicted with some in *silico* methods.

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P-4

Nicotinic Acid Derivatives of Some Triterpenes as Highly Effective Antiviral Compounds.

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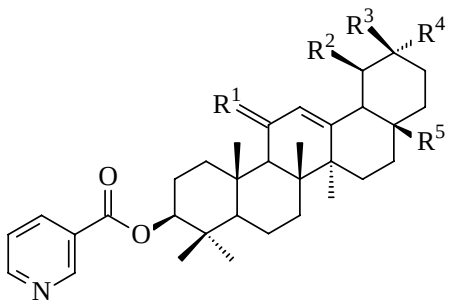
Five-members triterpenoid esterification is the perspective direction of new pharmacologically active derivatives obtaining. Natural products turn to be nowadays one of the most important and promissing source of new substances for drug development of varied directions of action. Triterpenoids present numerous group of compounds broadly distributed in plant kingdom and many of these substances presents interesting pharmacological types of action. The most promissing triterpenes with proved activity is Carbenoxolone, derivative of glycyrrhetinic acid with hepatoprotective activity [e.g. 1], antiviral betuline-derived Bevirimat with new mechanism of action [2, 3] or antiviral Niglizine [4]. Nicotinic acid is knowas a pharmacologically active compound with broad spectrum of action [5]. These reports, along with our own preliminary results that concerned triterpenes with potent antiviral activity, prompted us to embark on an investigation to modify the structure to improve the above mentioned activity.
In this paper we present the modification of oleanolic, glycyrhhetinic and ursolic acid with the usage of nicotinic acid and the results of screening tests towards antiviral activity.



	R^1	R^2	R^3	R^4	R^5
oleanolic acid	H_2	H_2	CH_3	CH_3	COOH
glycyrrhetinic acid	O	CH_2	CH_3	COOH	CH_3
ursolic acid	H_2	CH_3	H	CH_3	COOH

To obtain new highly active viral inhibitors, oleanolic, glycyrrhetinic and ursolic acids were subjected to reaction with nicotinic acid in boiling pyridine leading to derivative with blocked 3-hydroxy function. The structures of the obtained compounds were established on the basis of spectral data. The obtained compounds were tested towards antiviral activity.

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P-5

Studies on the Interactions Between DNA Topoisomerases and PAMAM-NH_2 Dendrimer – Modified Digoxin and Proscillaridin A Conjugates.

Anna Bielawska [a], *Katarzyna Winnicka* [b], *Bożena Popławska* [a], *Krzysztof Bielawski* [c]

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In contrast to conventional polymers, dendrimers are prepared by a stepwise synthetic procedure, leading to a highly regular branching pattern, well-defined architecture, and a very low polydispersity index [1,2]. Polyamidoamine (PAMAM) dendrimers, the most widely studied dendrimers, are recognized as a very promising kind of nanocarriers for many potential applications, such as delivery vehicles for drugs, DNA, and proteins. Their diameters increase with each generation, while molecular weight and number of functional surface groups double [1,2]. The functional surface groups make them very hydrophilic and highly water soluble. These surface functional groups are often used to covalently attach drugs, ligands or imaging agents for targeted delivery, controlled release, or imaging applications [1,2]. Cardiotonic steroids have long been and continue to be used in the treatment of congestive heart failure as positive inotropic agents. Epidemiological studies had shown that digitalis has also anti-cancer effects. Over the last 10 years, interest in developing cardiotonic steroids as anti-cancer agents has grown progressively [3]. The studies on the structure–activity relationship revealed that lactone in position 17β is crucial for the cardiotoxicity of digoxin and proscillaridin A. Therefore, we synthesized two compounds Dig and Prosc, derivatives of these glycosides containing the carboxylic group instead of the lactone moiety. In the present study Dig and Prosc were conjugated to G3 PAMAM-NH_2 dendrimer (with 32 primary amino groups on surface) via amide linkage [4]. To test whether cytotoxic properties were related to DNA-binding and topoisomerases action, these conjugates were evaluated in a cell-free system. While the parent drug - Dig inhibited only topoisomerase II at concentration 100 nM, PAMAM-Dig conjugate inhibited both topoisomerase II at lower 30 nM concentration and additionally inhibited topoisomerase I at the same 30 nM concentration. Prosc – as a parent drug was a potent poison of topoisomerase I and II at 100 nM and 30 nM, respectively, whereas PAMAM-Prosc inhibited either topoisomerase I and II at lower concentration of 30 nM.
While topo I is the specific target for only a limited group of drugs acting as poisons of the enzyme, such as camptothecin and derivatives, topoisomerase II is the primary target of poisoning by an increasing number of cytotoxic drugs of diverse nature currently available for the clinical treatment of human cancers [5]. Because of their central role in DNA replication, transcription and repair processes, topoisomerases II enzymes are important in both current and future strategies for cancer chemotherapy especially since overexpression of these proteins has been demonstrated in many human tumor types, such as breast cancer. There has been substantial interest in compounds that may act against both type I and type II topoisomerases. Dual topoisomerase poisons are of interest for their use in the treatment of cells exhibiting multi-drug resistance (MDR).

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P-6

The Effect of Dinuclear Platinium(II) Complex on Cell Signalling Pathways in Human Breast Cancer Cells.

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Continuous efforts are being made to broaden the spectrum of activity and to improve the therapeutic properties of platinum-based agents. Many researchers have turned to multi-nuclear platinum complexes in an effort to overcome both natural and acquired resistance to cisplatin in human cancer cell lines [1-3]. The adducts formed by multi-nuclear platinum complexes are vastly different from the adducts formed by cisplatin. It has been suggested that the distortions induced by these complexes are only weakly recognised by DNA repair proteins [1-3]. The present study was undertaken to extend our recent findings related to the antineoplastic activity of novel dinuclear platinum(II) complexes with berenil and amine ligands [4,5]. Berenil (1,3-bis(4'-amidinophenyl)triazene) can exhibit minor groove binding when it binds to both DNA and RNA duplexes, while also showing a preference for DNA duplexes with unobstructed minor grooves [6,7]. In this study, Pt_2(2-picoline)$_4$(berenil)$_2$ was expected to be localized in the vicinity of the DNA, and the combined effect resulting from platination and minor groove binding might confer the cytotoxic activity of Pt_2(2-picoline)$_4$(berenil)$_2$.
One of the characteristic features of breast cancer cells is a deregulation of their interaction with extracellular matrix proteins. Therefore, changes in the quantity, structure and distribution of collagens caused by anticancer agents may affect the metabolism and function of human breast cancer cells. Collagen biosynthesis and cell growth are stimulated by the insulin-like growth factor I (IGF-I). IGF-I, acting predominantly through the IGF-I receptor, has been demonstrated to stimulate proliferation, promote survival, enhance the metastatic potential of breast cancer cells and prevent apoptosis. The effects of Pt_2(2-picoline)$_4$(berenil)$_2$ on collagen biosynthesis, β_1-integrin receptor, IGF-I receptor and the expression of several proteins in the signal generated through the receptors like: phosphorylated MAP-kinases (ERK1/2 and p38), phospho Akt, NF-κB and the presence of apoptosis in human breast cancer cells were compared to those caused by cisplatin. The up regulation of β_1-integrin and insulin-like growth factor I (IGF-I) receptor expression by the complex was shown to be accompanied by an increase in the expression of mitogen activated protein kinases in breast cell lines. The phenomenon was related to the increased expression of nuclear factor-kappaB (NF-κB) by Pt_2(2-picoline)$_4$(berenil)$_2$ as shown by the Western immunoblot analysis. Flow cytometric analysis and a fluorescent microscopy assay demonstrated that cell death appeared to result from apoptosis, with the possibility of secondary necrosis. The data presented suggested that Pt_2(2-picoline)$_4$(berenil)$_2$ impaired growth and metabolism of breast cancer cells more efficiently than cisplatin. These results indicated also the different properties of Pt_2(2-picoline)$_4$(berenil)$_2$ and cisplatin.

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P-7

Synthesis, Anticonvulsant Activity and 5-HT_{1A}, 5-HT_{2A} Receptor Affinity of New N-(4-Arylpiperazin-1-yl)-propyl- Derivatives of 3,3-Disubstituted Pyrrolidine-2,5-dione.

Iwona Chlebek [a], *Jolanta Obniska* [a], *Krzysztof Kamiński* [a], *Beata Duszyńska* [b], *Andrzej Bojarski* [b], *Krystyna Nędza* [b]

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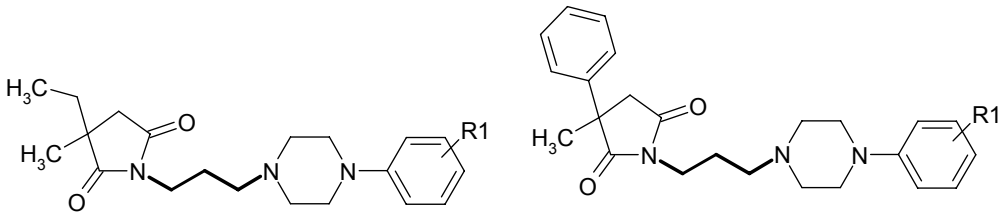
In the course of developing new potential anticonvulsant agents and 5-HT_{1A}/5-HT_{2A} receptor ligands we focused our attention on a group of 3-substituted-pyrrolidine-2,5-diones with a 4-aryl-piperazin-1-yl-alkyl fragment at the imide nitrogen atom. Between these compounds many derivatives exhibited anticonvulsant activity, as well as, higher affinity to 5-HT_{1A}/5-HT_{2A} receptors [1, 2].
In line with the above findings, in the present study we obtained two series of N-[(4-arylpiperazin-1-yl)-propyl]-3-methyl-3-phenyl- and 3-ethyl-3-methyl-pyrrolidine-2,5-diones. All the above mentioned compounds were tested *in vivo* for their anticonvulsant activity within the Antiepileptic Drug Development (ADD) Program, Epilepsy Branch, National Institute of the Neurological and Communicative Disorders and Stroke (NINCDS), Rockville, using procedures described elsewhere [3, 4]. The affinity of the investigated compounds for 5-HT_{1A} and 5-HT_{2A} receptors *in vitro* was assessed on the basis of their ability to displace [^{3}H]-8-OH-DPAT and [^{3}H]-ketanserin, respectively. The structures of the compounds synthesized are presented below.



R1 = H, 2-F, 4-F, 2-Cl, 3-Cl, 4-Cl, 3-CF_3, 2-OCH_3

This study was supported by the Polish MNiSW grant Nr N N405 298536 and by the Polish-Norwegian grant PNRF-103-AI-1/07

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P-8

Application of Mitsunobu Reaction for the Synthesis of Various Substituted 4-Amino-1-benzylpiperazine Derivatives.

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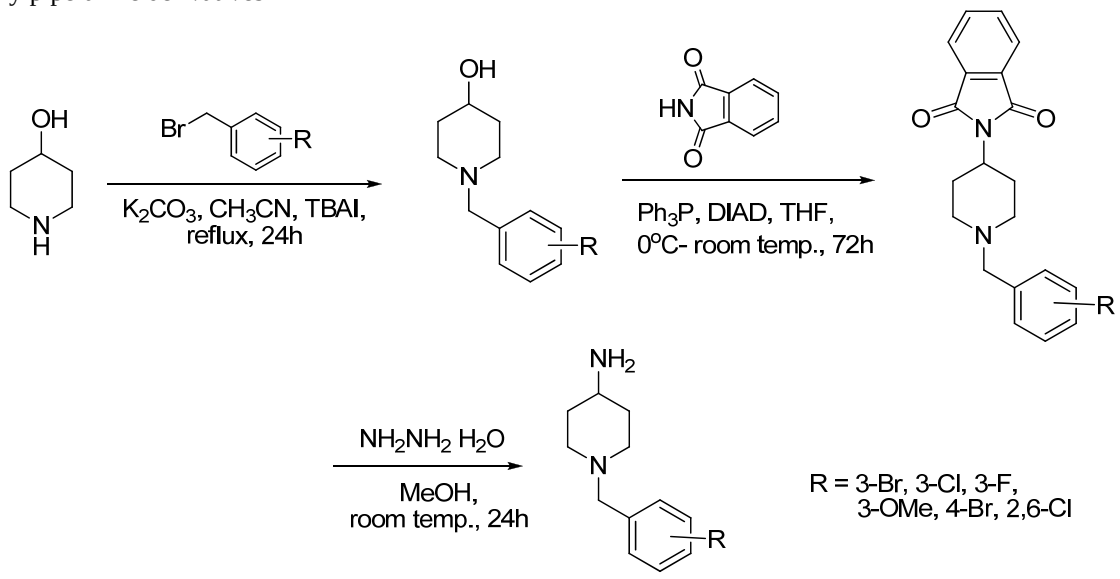
N-benzylpiperidine fragment is a pharmacophore, which is present in the structures of cholinesterase (AChE) inhibitors. Based on crystallographic and molecular study it was proofed this element interact with active site of AChE [1, 2].
As a continuation our research [3] directed acetylcholinesterase inhibitors, new derivatives of *N*-benzylpiperidine were designed. At the first step of this investigation a method of synthesis of 4-amino-1-benzylpiperidine was developed.
As a starting material for the planned synthesis 1-benzylpiperidin-4-ol was chosen. At the first stage this compound under condition of phase-transfer catalysis was *N*-alkylated with relevant benzylbromide derivatives. Then obtained compound was a subject of Mitsunobu reaction which was carried out using phtalimide, triphenylphosphine (Ph_3P) and diisopropyl azodicarboxylate (DIAD) in THF leading to various substituted 2-(1-benzylpiperidin-4-yl)isoindoline-1,3-dione [4]. Finally, upon workup by hydrazine hydrate, the primary amine was liberated giving various substituted 4-amino-1-benzylpiperazine derivatives.



The identity and the purity of compounds synthesized were confirmed using thin layer chromatography, ^1H NMR spectra and combustion analysis.
The compounds obtained will be used for the further synthesis of acetylcholinesterase inhibitors.

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P-9

New Isophosphoramide Mustard Analogues as Prodrugs for Gene Therapy.

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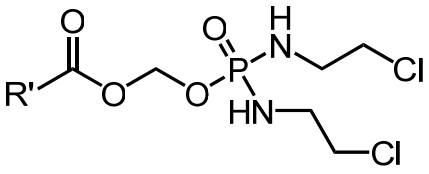
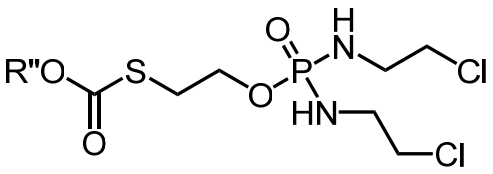
Isophosphoramide mustard (iPAM) is active, cytotoxic metabolite of ifosfamide (IF), anticancer alkilating drug widely used in the clinic. Poor selectivity of cytostatic drugs currently used in conventional cancer chemotherapy lead to attempts to employ gene therapy. One of this type therapy is Gene-Directed Enzyme Prodrug Therapy (GDEPT) [1]. This methodology requires prodrugs, which release highly cytotoxic drugs at the tumor after activation by an exogenous enzyme expressed in tumor cells.

Our research concentrated on new compounds, potential prodrugs for this therapy. These prodrugs need to satisfy a number of criteria. They must be efficient and selective substrates for the activating enzyme, and be metabolized to potent cytotoxins preferably able to kill cells at all stages of the cell cycle. Small molecules of prodrugs can be considered as comprised of two major domains, a “trigger” unit that is the substrate for the activating enzyme, and an “effector” unit that is activated or relased by this metabolic process, sometimes joined by a definable linker.

For this reason to obtain higher selectivity of cytostatic drugs we synthesized new ester analogs of iPAM with two different linkers, which can be activated by enzyme, carboxyesterase. Structures of potential prodrugs, analogs of N,N’-bis(2-chloroethyl)diamidophosphoric acid, were shown below:





R' = Me, *t*-Bu, Ph R" = Me, Et, *i*-Pr, Bz

Prodrugs for GDEPT should have a good stability under phisiological conditions. Hydrolytical stability of our potential prodrugs was examined. Now we are checking enzymatic activation and cytotoxic activity our analogs on several cell lines.

This research was supported by Nicolaus Copernicus University, Rector grant 70/2009.

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P-10

5-HT_{1A} Serotonin Receptors Affinity of Methoxybenzylidene Derivatives of Hydantoin.

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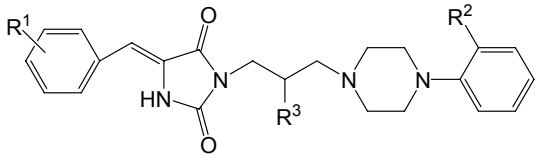
In recent years 5-HT_{1A} serotonin receptors have been the subject of intensive research because of their potential role in many diseases especially in depression mechanism. [1] The 5-HT_{1A} receptors are the family of G-protein-coupled seven-transmembrane helix receptors. Studies on receptor binding have shown that the numerous compounds with affinity for serotonin receptors contain arylpiperazine moieties. [2] In our research several 3-N-phenylpiperazine derivatives of 5-benzylidenehydantoin were designed, obtained and evaluated for their affinity to 5-HT_{1A} serotonin receptors. Such compounds have shown affinities for 5-HT_{1A} receptors in nano- to micromolar ranges.



R^1 = 3-OCH_3, 4-OCH_3, 3,5-diOCH_3, 3,4,5-triOCH_3
R^2 = OCH_3, OC_2H_5
R^3 = H, OH

Fig.1

This work was focused on the modifications of substituents at C5- and N3-hydantoin positions, respectively (**Fig 1**). The modifications of 5-arylidene fragment were concerned with number and positions of methoxyl substituents. As N3-modifications, 2-alkoxyphenyl piperazines, linked to hydantoin with propyl- or 2-hydroxypropyl chain, were obtained. The synthesis was divided into four steps: Knoevenagel condensation, Mitsunobu reaction, microwave irradiation and transfer of the obtained basic derivatives into the hydrochloric form. The new compounds were evaluated on their affinity for 5HT_{1A} serotonin receptors in radioligand binding assay using [^{3}H] 8-OH-DPAT as radioligand. SAR-sudies have shown the influence of C5- as well as N3- substituents on 5-HT_{1A} receptors affinity. In case of 5-arylidene fragments, mono-methoxyarylidene fragment was more profitable than di- or trimethoxyarylidene one. The strongest influence on the affinity was connected with alkyl linker at N3-position. An absence of hydroxyl substituent at propyl linker strongly increased affinities for 5-HT_{1A} for all investigated compounds. Affinities (K_i) for compounds with propyl linker (**R^3**=H) were in range of 20-164 nM, whereas the corresponding hydroxypropyl derivatives (**R^3**=OH) displayed affinities in range of 0.5-3.6 μM. The influence of 2-methoxy- and 2-ethoxy- substituent at phenylpiperazine phenyl ring was comparable.

This work was partly supported by grant: K/ZDS/000727.

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P-11

Influence of The Methoxy Substituent(s) of Arylidenehydantoin Derivatives on Their Affinity to α_1-ARs.

Anna Dela [a], *Małgorzata Dybała* [b], *Agata Siwek* [b], *Jadwiga Handzlik* [a], *Katarzyna Kieć-Kononowicz* [a]

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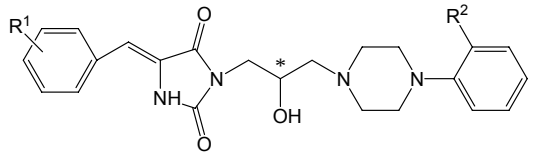
Recently, α_1-ARs have been the subject of intensive research taking into the account their potential role in arrythmias mechanism, especially in ischemic arrhythmia [1]. The α_1-adrenoreceptors are the family of G-protein-coupled seven-transmembrane helix receptors. Studies of receptor binding have shown that the numerous compounds with affinity for α_1-AR contain arylpiperazine moieties. In our previous research several N3-phenylpiperazine derivatives of diphenyl hydantoin were obtained [2, 3]. The compounds have shown affinity for α_1–ARs in submicromolar range (K_i). In our recent studies, new N3-phenylpiperazine derivatives of 5-arylidenehydantoin were obtained. They have shown high affinity for α_1-ARs. The most active structure (**Fig.1**) was chosen as a lead for the present investigation. In the present work, we designed new modifications of the arylidene hydantoin containing 2-alkoxyphenylpiperazine ring and modified 5-benzylidene fragment.



R^1: 3,4-diOCH_3
R^2: OC_2H_5

Fig.1

The chemical modfications were focused on an introduction of one-, two- or three methoxyl substituents at arylidene ring of the lead. The new compounds were obtained within four-step synthesis: (1) Knoevenagel condensation, (2) Mitsunobu reaction, (3) microwave irradiation and (4) transfer of the obtained basic derivatives into the hydrochloric form.
The new hydantoin derivatives were evaluated on their affinity for α_1-adrenoreceptors in radioligand binding assay, using [^{3}H]prazosin as selective radioligand. The assay indicated promising affinities for α_1-AR in whole tested population with Ki-values in similar range (65-187 nM). SAR-sudies displayed a profitable influence of alkoxyl substituent at both, aryl- and arylidene fragment on α_1-AR affinities. As the evaluated compounds contain chiral center within alkyl linker, enantiomers of a most active compound were synthesized. Binding assay for the enantiomers showed small differences in Ki-values for both enantiomers and corresponding racemic-compound. It suggests that hydroxypropyl linker is a structural fragment which does not participate in the interaction with α_1-AR.
The work was partly supported by grant: K/ZDS/000727.

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P-12

Evaluation of Mutagenic Properties of Some Triazine Derivatives, Ligands of Histamine H_4 Receptor, Using *Vibrio harveyi* Test.

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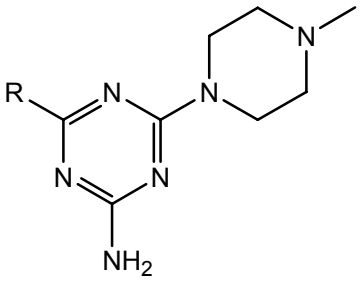
The recently characterized histamine receptor, named H_4 receptor (H_4R) is the promising target in the therapy of inflammatory diseases and disorders of the immune system [1]. To further explore the (patho)physiological function of the H_4R selective ligands are needed. In the group of substituted 4-(4-methylpiperazin-1-yl)-1,3,5-triazine derivatives some compounds have been recently described in patent literature as potent modulators of H_4R [2]. In addition to this, an increase in affinity to H_4R has been observed with additional amino group at the heteroaromatic ring of the structurally related 4-(4-methylpiperazin-1-yl)-pyrimidine derivatives [3]. Taking these structure-affinity relationships into account we have designed and synthesized a series of compounds combining both features: 4-(4-methylpiperazin-1-yl)-1,3,5-triazin-2-amine derivatives substituted in 6-position (Fig. 1).



R = CH_3 or substituted phenyl

These compounds were tested for their affinities at recombinant human H_4R transiently expressed in insect Sf9 cells and showed affinities in the (sub)micromolar concentration range. Nowadays, strong emphasis is put on eliminating non-druglike compounds at an early stage of drug development process [4]. Thus we assess the mutagenic activity of these compounds used the *Vibrio harveyi* assay. Four *Vibrio harveyi* strains were used: BB7 (natural isolate), BB7M (BB7 derivative containing *mucA* and *mucB* genes in the plasmid pAB91273, products of these genes enhance error-prone DNA repair), BB7X (BB7 derivative oversensitive to UV light) and BB7XM (created by transforming BB7X strain with the plasmid pAB91273).

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P-13

Preliminary Antiepileptic Activity Evaluation for Some 6-Methoxyxantone Derivatives.

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Epilepsy belongs to most common disorders of brain function and it still constitutes a great challenge in the fields of both clinical neurology as well as medicinal chemistry. It affects about 1% of world human population, including children, the elderly and pregnant women. Recurrent seizures significantly affect the quality of life of the patients. It is also worth to remember about increased prevalence of depression among people with epilepsy, which also results in reduction of quality of their lives. The main objective of pharmacotherapy of epilepsy is to control the seizures, including total elimination or limitation of their number. Despite continuous progress in the pharmacotherapy of epilepsy and introduction of new antiepileptic drugs, it is estimated that 30% of patients are still insufficiently treated. Moreover, the use of antiepileptic drugs is associated with multiple and often serious adverse effects [1-5].
Based on the previous results of our research dealing with compounds with anticonvulsant activity it can be concluded that one of the interesting group of substances are xanthone derivatives. Among them compounds possessing aminoalkanol moiety deserve special attention. Some of them posses good values of ED_{50} in the MES test after intraperitoneal administration in mice and good values of the calculated index of protection (PI). For example, for (*R,S*)-1-(6-methoxy-2-xanthonemethyl)-amino-2-propanol and S-(+)-2-(-6-chloro-2-xanthonemethyl)-amino-1-propanol ED_{50} and PI values were 37.4 mg/kg, 2.56, 72.97 mg/kg and 6.85 respectively [6, 7].
As a continuation of our former work we herein report on the results of preliminary evaluation of anticonvulsant activity of a series of corresponding 6-methoxyxanthone derivatives, including the enantiomers of compounds previously studied as racemates. Pharmacological studies were carried out according to the Antiepileptic Drug Development Program (ADD) at National Institutes of Health (NIH) in Rockville, USA [5]. All compounds were screened in the maximal electroshock (MES) and subcutaneous pentylenetetrazole (scMet) induced seizures tests as well as for neurotoxicity (TOX) in the rotarod test in mice after *i.p.* administration. 12 of the tested compounds showed activity at the dose of 100 mg/kg, 2 at the dose of 300 mg/kg in the MES test (0.5 h; mice; *i.p.*). In the scMet test one compound showed its activity at the doses of 30 and 300 mg/kg (0.5 h; mice, *i.p.*). 10 compounds were also screened in the MES test as well as tested in the neurotoxicity assay following oral administration in rats at the dose of 30 mg/kg. 9 of 10 substances showed some anticonvulsant activity. Compounds **1** and **2** were also tested in the quantitative assays of MES and neurotoxicity after intraperitoneal administration in mice. The values of ED_{50} and TD_{50} were calculated for them, they were for **1**: 107.26 mg/kg and 269.27 mg/kg (PI = 2.51), for **2:** 47.57 mg/kg and> 400 mg/kg (PI> 8.41), respectively.

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P-14

N-Benzyl Substitiuted 2-(4-(Diphenylmethylene)piperidin-1-yl)-4-hydroxybutanamides as a Potential GABA Uptake Inhibitors.

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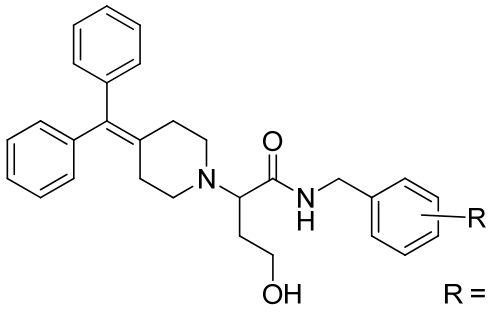
A number of central nervous system disorders have been linked to hypoactivity in inhibitory neurotransmission elicted by γ-aminobutyric acid (GABA). In addition to the treatment of anxiety and sleep disorders, drugs that enhance GABA-mediated inhibition have been found highly effective in the management of seizures disorders .
Since GABAergic neurotransmission is terminated by uptake into neuron or surrounding glia cells, inhibitions of GABA transporters responsible for uptake would prolong the GABAergic signal in a use-dependent manner, therereby counteracting GABA hypoactivity. Although many GABA uptake inhibitors possess antiepileptic properties only Tiagabine has been approved so far for the treatment of epileptic disorders [1,2].
As part of an ongoing project with the aim to developed GABA uptake inhibitors a series of γ-hydroxybutyric acid (GHB) was designed. As parent compound the γ-hydroxybutyric acid amides in which the diphenylmethylene-piperidin-1-yl functionality resides in 2 position of the GHB. Variation of the position of amide functionality was expected to shed some light on the structure-activity relationship for that class of compounds.



R = H, Cl, F, OMe, Me

It was found the compounds obtained are non-selective GABA uptake inhibitors. The determined for them pIC_{50} values are in range 4.42-5.01 (GAT-1), 4.12-4.71 (GAT-2), 4.25-4.55 (GAT3) and 4.17-4.75 (GAT-4).
In order to defined structure-activity relationship within group of compounds tested their lipophilicity was determined using reversed phase thin layer chromatography.

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Acknowledge
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P-15

5-Hydantoin Derivatives as Potential Efflux Pump Inhibitors.

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Multidrug resistance has become a factor seriously limiting treatment of various diseases, including bacterial infections therapy, but also antifungal and anticancer treatment [1-3]. Bacteria are able to efficiently decrease the antibiotic activity by using following resistance mechanisms: (1) By-passing efflux activity: improving the molecular design of old antibiotics to reduce their efflux; (2) direct action on the permeability of the bacterial cell envelope: decreasing the efficacy of the membrane barrier; (3) Blocking the efflux capacity of bacterial cell: alteration of pump function. The (3)-mechanism gives a new research area for medicinal chemistry to design and synthesize new compounds able to inhibit protein efflux pumps of pathogenic bacteria. This new class of therapeutic compounds would be effective on MDR infectious bacteria and can be used as an « adjuvant » that improves the intracellular bacterial concentration of known antibiotics. Our recent-years researches gave several groups of hydantoin derivatives that can be considered as potential anti-MDR agents Results of our previous study indicated that 5-arylidene-2-thiohydantoins showed promising efflux pump inhibition (EPIs) properties in *E. aerogenes*. The present work is focused on small hydantoin derivatives possessing at 5- position (hetero)aromatic substituents (**Fig. 1**)

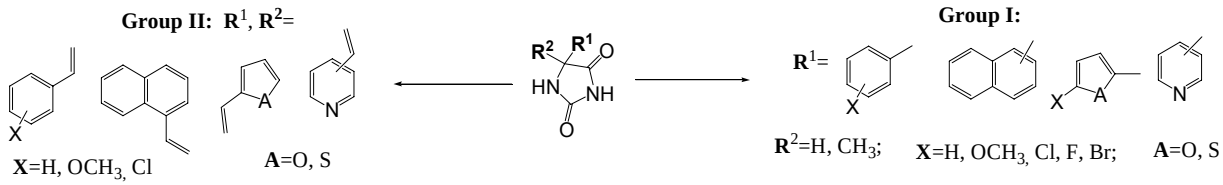

Fig. 1. General structure of the investigated 5-substituted hydantoins

The compounds were obtained within 1-step synthesis including Bucherer-Bergs reactions or various Knoevenagel condensations. Selected compounds were assayed on their EPIs activity in two *E. aerogenes* strains: ATCC13048 as reference and the derivative CM64 strain which over produces AcrAB-TolC efflux pump. Three following antibiotics were used: chloramphenicol, sparfloxacin and nalidixic acid. Results indicated that 5-arylhydantoin derivatives showed weaker EPIs properties than those of 5-arylidene-2-thiohydantoins.

The work was partly supported by grants: 501/N-COST/2009/0 (K/PMN/000031), COST action BM0701.

* The student from Rheinische Friedrich-Wilhelms-Universität Bonn, D BONN01, the work performed within Erazmus-Socrates program

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P-16

Synthesis and Mutagenic Properties of New Hydantoin Derivatives with Potential Anti-MDR Activity.

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One of the reasons of re-emergence of infectious diseases, observed for last decades, is the increasing resistance of pathogenic bacteria to available antibiotics. The multidrug resistance (MDR) is a factor seriously limiting treatment of various bacterial diseases as well as antifungal and anticancer treatment [1, 2]. One of the ways to combat MDR is searching for new chemical compounds that are able to inhibit protein pump system responsible for drug efflux. This new class of therapeutic compounds can be used as an effective « adjuvant » that supports the target drug action by increase its concentration in a target cell. During the search for new adjuvants, it is important to consider compounds which are anti-MDR-active and, simultaneously, their toxicity risk should be low. On the other hand, aromatic hydantoin derivatives seem to be an interesting target in pharmacological strategies for overcoming multidrug resistance. Recent studies distinctly identified and described a presence of benzyl-hydantoin binding site in protein transporters (nucleobase–cation–symport-1 transporters, Mhp, from *Microbacterium liquefaciens*) [3]. Basing on this, several hydantoin derivatives (Fig.1) were designed and synthesized as potential anti-MDR agents.

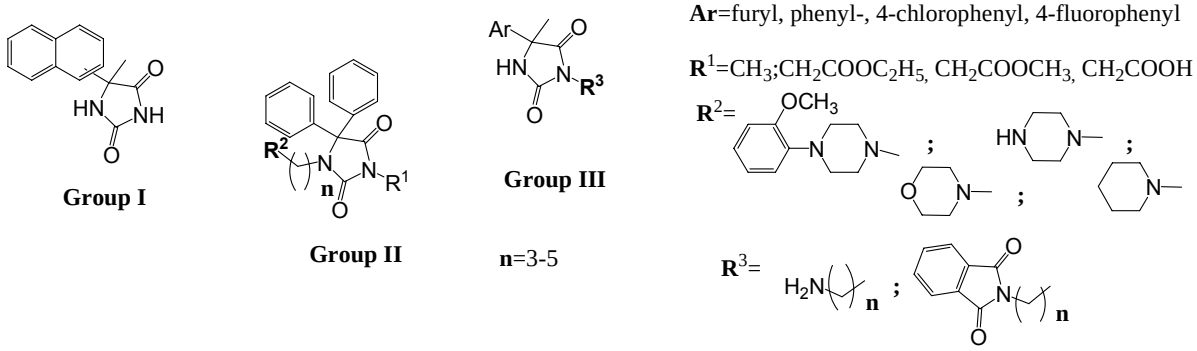

Fig. 1. Structure of the tested hydantoin derivatives

The compounds were obtained within 1-3-step synthesis including various alkylations and Gabriel's synthesis. All compounds were investigated on their toxicity risk *in silico* using three models of toxicity (mutagenic-, tumorigenic- and reproductive effective- properties). Selected compounds were tested on their mutagenicity *in vitro* with applying the assay by using the *Vibrio harveyi* strains.

Authors thank to Prof. Grzegorz Węgrzyn from University of Gdańsk for *Vibrio harveyi* strains. The work was partly supported by financial programs: K/ZBW/000473 and K/PMN/000031.

* The student from Rheinische Friedrich-Wilhelms-Universität Bonn, D BONN01, the work performed within Erazmus-Socrates program.

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P-17

Synthesis and Evaluation of Potential Mono- and Bivalent Ligands of Adenosine A_{2A} Receptors.

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Studies in thast few years have shown that GPCR receptors (G-protein Coupled Receptors) may form homo- and heterodimeric structures. For example dopamine, adenosine or opioid receptors may form homodimeric structures or different types of adenosine (especially A_{2A}) and dopamine (D_2 dopamine) receptors may form heterodimers.

The aim of this study was synthesis of dimer and monomer derivatives of pyrimido[2,1-f]purinediones as potential ligands of A_{2A}-adenosine receptors.

The substrates for synthesis were bromoethyl- and bromopropylpyrimidopurinediones. These substances were treated with 4-benzylamines (4-chloro, 4-methyl, 4-methoxy) in fusion reaction with ues of the microwaves. As the result of this reaction ten compounds were obtained. Five of them were recognized as dimeric and five as monomeric. For the synthesized compounds, in order to confirm their structures ^{1}H NMR, IR and elemental analyses were performed. In spite of the problem with solubility, especially for dimeric species, for one compound x-ray structure analysis was done (Fig. 1).

This work was partly supported by grant N405 297 836.

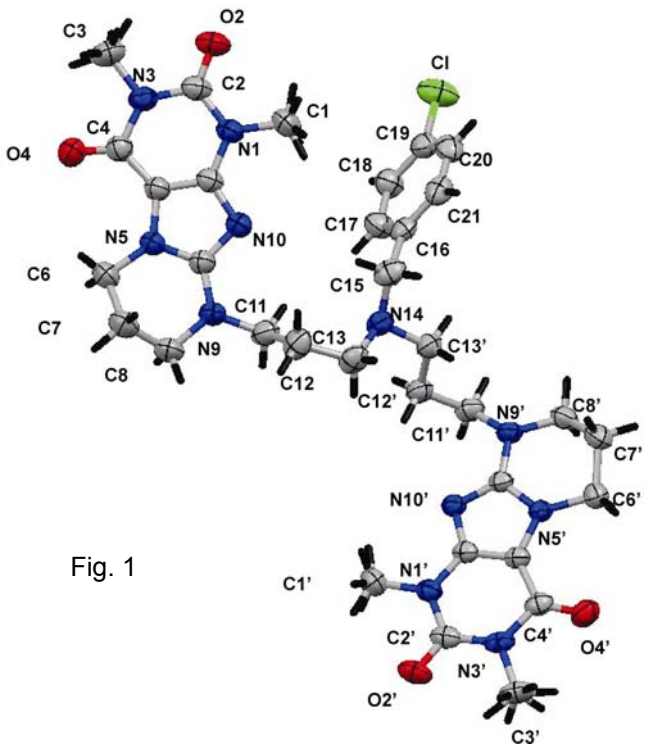

Fig. 1

P-18

Determination of pK_A Values of Potential Drugs Using ^1H NMR Spectroscopy and Capillary Zone Electrophoresis.

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The acid dissociation constant is an important physicochemical parameter of a potential pharmaceutical substance, and knowledge of it is of fundamental importance in a wide range of applications and research areas. It governs solubility, absorption, distribution, metabolism and elimination.

Acid dissociation constant of four 3-{[2-(4-fluorophenoxy)ethyl]amino}-2-hydroxypropyl 4-alkoxy-benzoate derivatives, substances with potential ultra short β- and α-adrenolytic effect, have been determined from ^1H NMR chemical shifts changes versus the pH of the buffer. Nonlinear least-squares fits were used for assessment pK_a values.

Due to low solubility of investigated compounds in water, measurements were provides in mixture of D_2O/methanol. Values of pK_a were recalculated for water and it was also necessary to recalculate pK_a values measured in deuterium water to water medium.

pK_a values determined by ^1H NMR titration were compared to those reported using capillary electrophoresis. The determination of pK_a values by CE is based on observation of the effective mobility of an ionizable compound in a series of electrolyte solutions of constant ionic strength and various pHs. Dissociation constants were evaluated by application of least square method to nonlinear regression of mobility curves.

The good agreement of the results is evidence that either technique is suitable to perform pK_a measurements.

For comparing the variance between ^1H NMR and CZE methods, Snedecor criterion was used.

This work was supported by the Grant Project IGA 23/2010/FaF VFU Brno.

P-19

A Thermodynamic Study of the Partitioning of the Potential Drugs into Water/Octanol and Water/Cyclohexane Solvent Systems.

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Knowledge of the partition coefficient of potential drugs is important for prediction of their pharmacokinetic and pharmacodynamic properties and it makes possible to estimate potency of substances to achieve expected effect. Drug lipophilicity is key factor for its absorption, distribution and elimination.

The partition coefficients of three 4-{2-[(2-hydroxy-3-(4-alkylcarbamoylphenoxy)propyl)amino]ethyl}-phenoxyacetic acid derivates with potential β-adrenolytic effect were determined by shake flask method in two partitioning systems; octanol/buffer and cyclohexane/buffer. Determinations were performed at four temperatures; 25 °C, 30 °C, 35 °C and 40 °C whereas the samples were incubated for 24 hours. Partition coefficients were calculated from the concentration variations of substances before and after shaking. For quantifying concentrations of substances ultraviolet spectrophotometry was used.

The octanol/buffer system serves as a reference partitioning system and well correlates with partitioning and bonding to blood proteins. On the other hand cyclohexane as non-polar solvent, which interacts only by non-specific forces (London interactions), assigns better correlation with partitioning in biological membranes.

Correlations between log P in octanol/buffer and cyclohexane/buffer systems were evaluated and the relationship between the logarithms of partition coefficients were expressed using Seiler's equation. Based on the calculated Gibbs energy change in distribution between the two phases were discussed possible mechanisms of distribution. The entropy and the enthalpy of transfer were also calculated. The van't Hoff plots (the temperature dependence of partitioning coefficients) were created. In all cases, straight lines with correlation coefficients *r* near to 0.95 were obtained for both partitioning systems. The ability of substances to pass through biological membranes was predicted from the results of the thesis.

P-20

Stable Expression of Fluorescently Tagged A_{2A} Adenosine Receptor in HEK 293 Cells.

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The adenosine receptor (AR) family consists of four G protein-coupled receptor subtypes: A_1, A_{2A}, A_{2B} and A_3 [1]. Adenosine A_{2A} receptors (A_{2A} ARs) play an important role in regulating smooth and well-coordinated movement. There is now evidence that A_{2A} AR ligands may provide a novel therapy for the treatment of Parkinson's disease with lower risk of dyskinesias and may exhibit neuroprotective effects [2, 3]. Due to the importance of A_{2A} ARs there is a need of developing the reliable models for investigation of molecular pharmacology of the mentioned receptor.
In this study it was our aim to achieve a stable expression of human A_{2A} adenosine receptors tagged with a fluorescent protein in HEK 293 cells. For that purpose gene encoding hA_{2A} AR was firstly cloned into the plasmid pEYFP-N1 containing the cDNA sequence of enhanced yellow fluorescent protein (EYFP). This construct was then introduced into human embryonic kidney cells (HEK 293) using FuGene HD reagent and transfected cells were subjected to selection with geneticin (G418). Stable expression of the fusion protein was indicated by means of fluorescence microscopy and flow cytometry. In order to verify functional integrity and activity of the expressed receptor proteins radioligand saturation studies were performed with the use of selective A_{2A} AR ligand [^{3}H]CGS21680. The K_D value obtained in that experiment was comparable to the literature data [4].

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P-21

The Structural Characterization of 2-{2-[4-(2-Fluorophenyl)-piperazin-1-yl]ethyl}-5,7-dimethyl-6-phenyl-1,2,3,4-tetrahydro-6*H*-pyrrolo[3,4-*d*]pyridazine-1,4-dione, New Potential Analgesic Agent.

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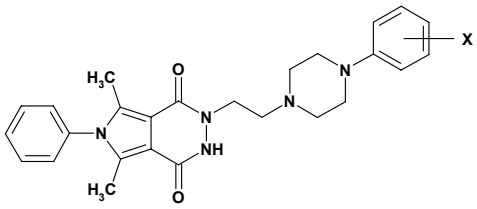
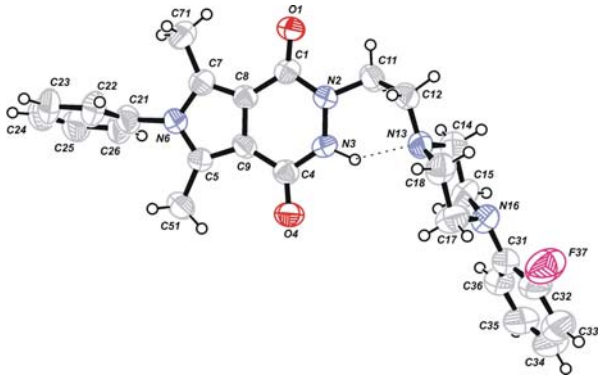
The 2-{2-[4-(substituted-phenyl)piperazin-1-yl]ethyl}-5,7-dimethyl-6-phenyl-1,2,3,4-tetrahydro-6*H*-pyrrolo[3,4-d]pyridazine-1,4-diones were synthesized as the potential analgesic agents.



The structure of the compounds was unambiguously established by X-ray crystallography, taken 2-{2-[4-(2-fluorophenyl)piperazin-1-yl]ethyl}-5,7-dimethyl-6-phenyl-1,2,3,4-tetrahydro-6*H*-pyrrolo[3,4-*d*]pyridazine-1,4-dione (X = 2-F) as model compound.



The conformation and steric orientation of the side chain is stabilized by an intramolecular hydrogen bond N3-H...N13 [N3-H = 0.99(7), H...N13 = 1.98(8), N3...N13 = 2.848(8) Å, N3-H...N13 = 146(6)^{o}]. Due to the tautomerization of the pyridazinone moiety the tautomeric equilibrium within a series of pyrrolo[3,4-*d*]pyridazines were analysed using the theoretical calculation at DFT/B3LYP/6-311++G(d,p) level.

P-22

In vitro Cytotoxic Properties of Two Novel Flavonone-Based Ruthenium Complexes.

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The complexes of transition metals, especially platinum play significalt role in the treatment of various cancers. The first and most popular metal-based drug – cisplatin has many severe side effects and many tumors have or develop resistance to the drug. There is need of finding new similar compounds with better therapeutic profile. During last years the ruthenium compounds attracted attention of many scientists as potentially effective and less toxic anticancer agents than cisplatin.
Two novel flavanone-based ruthenium complexes were synthesized and their structure were examined as well as their cytotoxic activity *in vitro* towards cancer cells and healthy human lymphocytes. The two compounds have high cytotoxicity towards human bladder cancer cells, both sensitive and resistant to cisplatin. They have also higher proapoptotic activity in these cell lines than cisplatin. On the other hand they are less toxic for healthy human lymphocytes *in vitro* than cisplatin.
The above mentioned results are encouraging to further research, because the pilot pre-clinical study show good potential cytotoxic activity of examined compounds and their possible lower toxicity for healthy cells than cisplatin.

P-23

Antiparkinsonian Effects of Novel Adenosine A_{2A} Receptor Antagonists.

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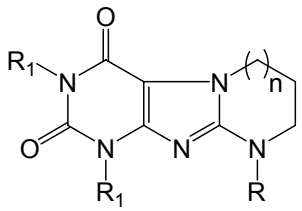
Parkinson's disease (PD) with its characteristic signs as bradykinese, akinese, tremor, catalepsy and cerebral disfunction is the most frequent among neurodegenerative diseases. While dopamine was long been the neurotransmitter most closely associated with PD, several other neurotransmitters active in the basal ganglia are also affected [1]. Recent studies have indicated that adenosine neurons modulate the activity of striatial projection neurons and are thus in a key positions to affect the overall function of the basal ganglia [2]. There is now accumulating evidence that adenosine A_{2A} receptor antagonists may provide a novel therapy of PD [3].
In our research efforts have been directed toward the study of novel selective ligands for A_{2A} AR_S based on xanthine molecule. Various tricyclic annelated xanthines: imidazo, pyrimido and diazepinopurinediones with different substituents were obtained [4,5] (Fig.1) and evaluated for A_{2A} AR_S affinity, displaying high submicromolar activity.



n = 0, 1, 2

R_1 = CH_3 ,

R = alkyl, cycloalkyl, aryl, (un)substituted arylalkyl

In this work we focused on the examination of the most active ligands for antiparkinsonian effects in rodent model of Parkinson's symptoms.

The dopamine D_2 antagonist haloperidol was used to induce catalepsy. The performed preliminary test indicated that some pyrimidopurinediones demonstrated antiparkinsonian effects, producing a significant reduction in catalepsy at each dose.

Partly supported by Polish Ministry of Science and Higher Education: grant NN 405 297 836

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P-24

Synthesis and X-ray Studies of Novel Porphyrazines Possessing Peripheral Pyrrolyl and Dimethylamino Groups.

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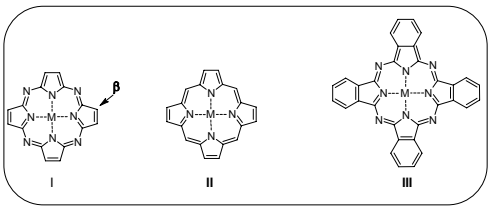
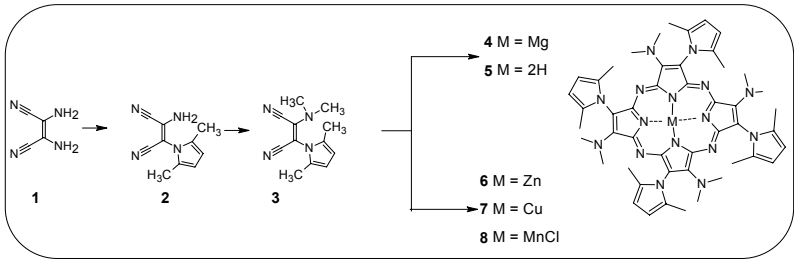
INTRODUCTION

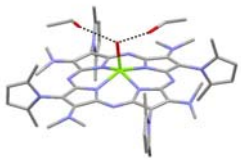


Peripherally functionalized porphyrazines **I** form a distinct class of novel macrocycles, along with the functionalized porphyrins **II** and phthalocyanines **III** (Figure). The porphyrazine (pz) macrocycle is isoelectronic with porphyrine, but in comparison it has substantially different electronic properties. The first possibility to modify pz is to substitute the core with metal entities (M), while the second one is connected with peripheral modifications. Pzs substituted in the periphery possess many potential applications as photosensitizers in photodynamic therapy, sensors, molecular semiconductors and non-linear optical materials [1].

RESULTS

The Paal-Knorr reaction of diaminomaleonitrile **1** with 2,5-hexanedione led to 2-amino-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-2(*Z*)-butene-1,4-dinitrile **2** [2]. This product was methylated to novel dinitrile **3**, which was successfully utilized in the Linstead macrocyclization towards magnesium symmetrical porphyrazine **4** as the major product (Scheme). Demetallation of **4** by removal of the magnesium ion gave the free base porphyrazine **5**. Macrocyclization reaction of **3** in pentanol and DBU as a base using various metal salts, like $Zn(OAc)_2$, $CuCl_2$ and $MnCl_2$ gave pzs **6**, **7** and **8**, respectively [3].





X-ray structure of **4**

The structure of porphyrazine-Mg complex **4** was determined by X-ray crystallography. The single crystal analysis showed that **4** is a symmetrically substituted porphyrazine derivative with 2,5-dimethylpyrrolyl and dimethylamino groups located alternately in the *β*-positions of the macrocycle (Figure). The pyrrole substituents are oriented nearly perpendicular to the porphyrazine core, whereas the dimethylamino groups are situated in the plane of the macrocycle platform.

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This study was supported by STN grant from the University of Medical Sciences in Poznań, SBN 502-05-03313427-50528.

P-25

Synthesis, Photophysical Properties and Photocytotoxicity of Phthalocyanines Possessing Non-Peripheral Ester-Alkyloxy Substituents.

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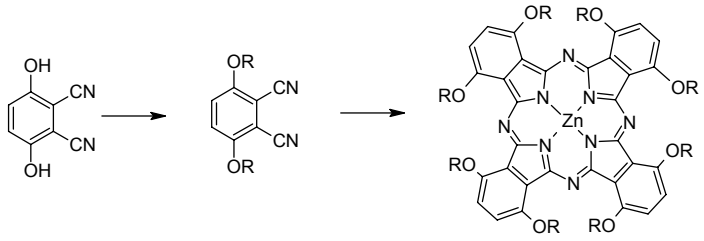
Phthalocyanines are synthetic aza-analogues of porphyrins. Their ability to generate the reactive oxygen species, mainly singlet oxygen, provides an opportunity to employ these macrocycles in the photodynamic therapy (PDT). Low solubility is the main hindrance preventing their wider usage in the therapy.



1 **2** R = $CH_2COOC_2H_5$ **3** R = $(CH_2)_3COOC_2H_5$ **Pc-4** R = $(CH_2)_3COOC_5H_{11}$ **Pc-5** R = $(CH_2)_3COOC_6H_{13}$

2,3-Dicyanohydroquinone (**1**) was employed in the synthesis of novel dinitriles **2** and **3** [1]. Dinitrile **2** decomposed under macrocyclic reaction conditions. Macrocyclization of dinitrile **3** performed in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base and zinc acetate in pentanol or hexanol resulted in **Pc-4** and **Pc-5**, respectively. During macrocyclization reaction the transesterification reaction occurred within the peripheral ester-alkyloxy chains.
Photostabilities of the compounds **Pc-4** and **Pc-5** were assayed under irradiation at a wavelength from the Q band in DMSO and DMF solvents. The compounds in DMSO solutions were found not to undergo photodegradation after exposure to irradiation. Photodecomposition of the macrocycles **Pc-4** and **Pc-5** in DMF was found to proceed according to the first order kinetic reaction in two stages. Quantum yields of singlet oxygen generation were determined using 1,3-diphenylisobenzofurane as the singlet oxygen quencher and zinc phthalocyanine (**ZnPc**) as a reference. Singlet oxygen quantum yields in DMSO were found almost identical for **Pc-4** and **Pc-5** and lower than that of **ZnPc**. However, in DMF **Pc-4** was superior to both **Pc-5** and **ZnPc**.
The photodynamic activity of **Pc-4** was tested against the cells of human squamous carcinoma. The toxicity of the compound was evaluated without light and after exposition to certain doses of radiation. The reference compound was unsubstituted **ZnPc**. The phototoxic effect generated by **Pc-4** was smaller than that of the standard. **Pc-4** was less effective than **ZnPc**, due to its hydrophobicity and aggregation.

P-26

The Polyphenol Glycosides Having Calcium Complexing Properties.

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Kidney stone disease, *nephrolithiasis*, is a chronic illness consisted in occurrence hardened mineral deposits in urinary system, called kidney stones. The stones form in effect of precipitating from the urine salts insoluble in water. They mostly consist on calcium salts [1,2]. Nowadays, on the pharmaceutical market there are no medicines for kidney stone disease. The drugs prescribed for the patients have only pain control properties, alternately regulate metabolism or increase the flow of urine [3]. In the 70th there were applied medicines dissolving kidney stones, *Rubiolizyna* and *Rubinex*, nevertheless there were found mutagenic substances in their composition and they were withdrawn from the medicine. The drugs contained hydroxyketone derivatives that dissolved kidney stones by forming complexes with calcium ions. What is more, sugars also create complexes with calcium ions [4,5].

On the faith of these assumptions we synthesized glycoside derivatives of hydroxyanthraquinones, maily alizarine glycosides, and other polyphenol glycosides having potential calcium complexing properties (Fig. 1). Their positive influence on dissolving model kidney stones, as well as surgical ones, were confirmed *in vitro* by the conductometric analysis and the flame photometry.

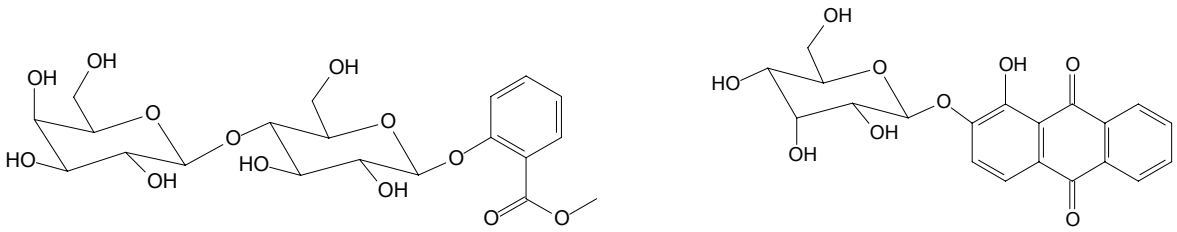

Fig.1. Methyl salicylate lactoside and alizarine glucoside.

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P-27

Docking of para-*t*-Pentylphenoxyalkyl Piperidine Derivatives and Fluorescent H_3 Receptor Ligand KF-1 to Histamine H_3 Receptor Homology Model.

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Histamine H_3 receptors are constitutively active G_i-protein coupled receptors mostly expressed in CNS, described as presynaptically located auto- and heteroreceptors. Activation of these receptors results in modulation of histamine levels, as well as that of other neurotransmitters such as: ACh, NA, 5-HT. Therefore blockade of these receptors could be useful in the treatment of different CNS disorders [1].
First known histamine H_3 receptor antagonists contained an imidazole group, which may be responsible for a number of side effects, due to its interaction with cytochrome P_{450}. Among others, one of the first successful imidazole replacements has been performed by piperidine moieties. According the proposed pharmacophore for histamine H_3 receptors, heterocyclic residue should be connected via the aliphatic linker with polar moiety, connected itself by other linker with the lipophilic residue.
For our research we used novel obtained and described in our group, para-*t*-pentylphenoxyalkyl piperidine derivatives, as well as previously described fluorescent ligand KF-1, containing NBD as a fluorescent marker[2]. The compounds used for this study were previously evaluated for histamine H_3 receptor activity *in vitro* in a binding assay for the histamine hH_3 receptor stably expressed in HEK-293 cells. Presented compounds show very good affinities.
Paying attention to the results described in literature [3] compounds were docked to histamine H_3 receptor model described by the group of Levoin. For this purpose Schroedinger MacroModel 9.7 suite was used.

Acknowledgements:
This work was partly supported by the Polish Ministry of Science and Higher Education Grants No: N N405 266 837, and DAAD/55/2007

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P-28

Optimisation of Dextromethorphane N-Demethylation Process.

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Dextromethorphan (DXM) has been used as an antitussive drug for more than 30 years. It is an uncompetitive NMDA receptor antagonist, σ_1 and σ_2 sigma receptor agonist, $\alpha_3\beta_4$-, $\alpha_4\beta_2$-, and α_7-nACh receptor antagonist, μ-, δ-, and κ-opioid receptor agonist. This makes DXM skeleton an interesting candidate for synthetic modification in searching for new medicines. The aim of this study was to improve the yield and purity of N-desmethyldextromethorphan, an important intermediate in further modification steps. Several different conditions were evaluated in order to find the most satisfactory one. New derivatives of DXM are expected to have anti-addictive properties.

P-29

Synthesis, Characteristics and Optical Sensor Property of Novel Porphyrazines Possessing Bulky Peripheral Thiol Substituents.

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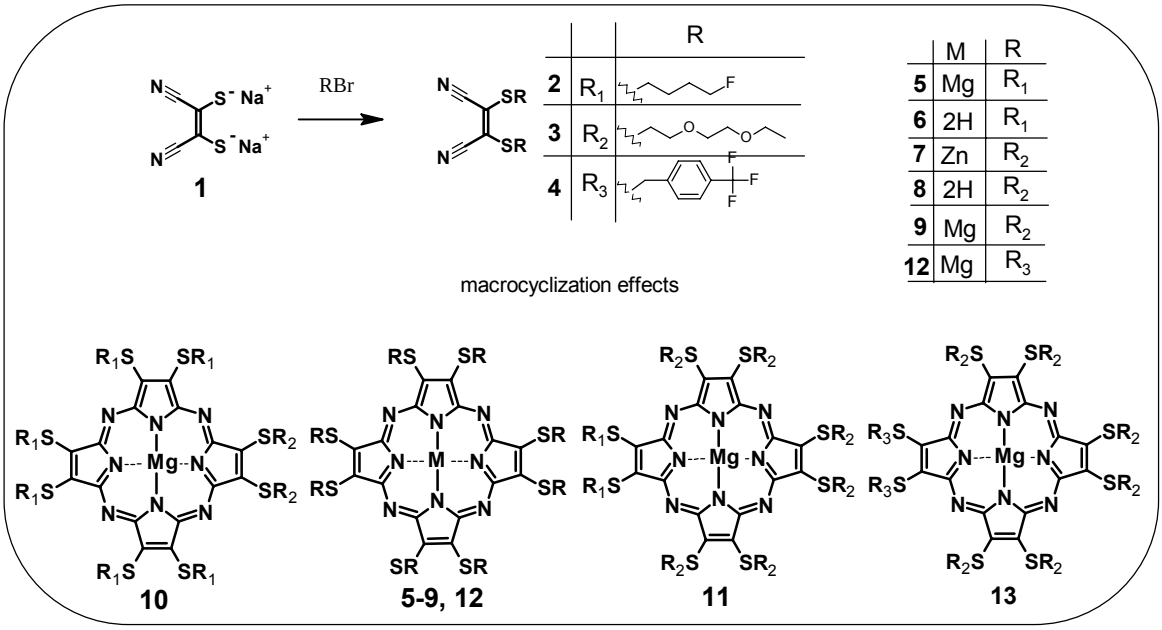
Porphyrazines (pzs) are aromatic macrocyclic compounds built of four pyrrolic rings linked together with azomethine groups. Thiol-derivatized pzs possess promising biological activity in photodynamic therapy. According to *in vitro* studies the strength and selectivity of phototoxic effect within these macrocycles can be modified by balancing among lipophilic and hydrophilic character of functional groups at the periphery [1]. Peripheral modification of these pzs with ether groups can improve their solubility in water, whereas fluorinated alkyl groups enable their *in vivo* imaging using ^{19}F NMR [2]. The aim of our research was to elaborate the synthesis of thiol-derivatized porphyrazines and prove their ability to coordinate palladium cations [3].



Alkylation of dimercaptomaleonitrile disodium salt **1** gave dinitriles **2**-**4** (Scheme), which were converted into symmetrical **5**, **9**, **12** and unsymmetrical magnesium pzs **10**, **11**, **13** using magnesium butanolate in butanol. Additionally, demetallated pzs **6, 8** and zinc pz **7** were synthesized. All macrocycles were characterized by both UV-vis and MS MALDI.

The ability of synthesized pzs to coordinate metal cations was determined by monitoring the UV-vis spectral changes during titrations with Pd^{2+}.

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P-30

Convenient Way of Synthesis and Crystal Structure of JNJ 7777120.

Dorota Łażewska [a], *Janina Karolak-Wojciechowska* [b], *Beata Kolesińska* [c], *Zbigniew Kamiński* [c], *Katarzyna Kieć-Kononowicz* [a]

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Histamine H_4 receptor (H_4R), discovered in 2000 independently by a few groups, is widely expressed on cells involved in immune response and inflammation. Anti-H_4R ligands, have been proposed to be useful in anti-inflammatory and immune modulating therapy [1]. As the first orally active, potent and selective non-imidazole H_4R antagonist was described JNJ 7777120 by Johnson & Johnson in 2003 [2]. JNJ 7777120 displayed K_i for the human H_4R of 4 nM, oral bioavailability of ~30% in rats and 100% in dogs. JNJ 7777120 has become a commonly used H_4 antagonist for probing the physiological role of H_4R. For example, JNJ 7777120 has been reported to have anti-inflammatory activity in vivo, inhibition of pruritus and allergic contact dermatitis, and exhibited anti-nociception in animal models of inflammatory and neuropathic pain. The synthesis of JNJ 7777120 was described some time ago. 5-Chloroindole-2-carboxylic acid was coupled with *N*-methylpiperazine in presence of HATU, HOAT and *N*,*N*-diisopropylethylamine (DIPEA) in DMF.[2] The described reagents are expensive so we attempted to find a new and more convenient way of preparation of this compound. As an alternative coupling reagent was used the known from many years carbonylodiimidazole (CDI) [3] and more recently described in literature *N*-triazinylammonium tetrafluoroborate [4]. Crystalographic studies of JNJ 7777120 show that in this structure crystallographic unit consists of three independent molecules which did not fit to each other exactly.

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P-31

The Polimorphism of Imatinibe® Mesylate.

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Imatinib mesylate chemically known as 4-[(4-Methyl-1-piperazinyl)methyl-N-[4-methyl-3-[[(4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamine methanesulfonate is represented by the following structural formula (Fig. 1).

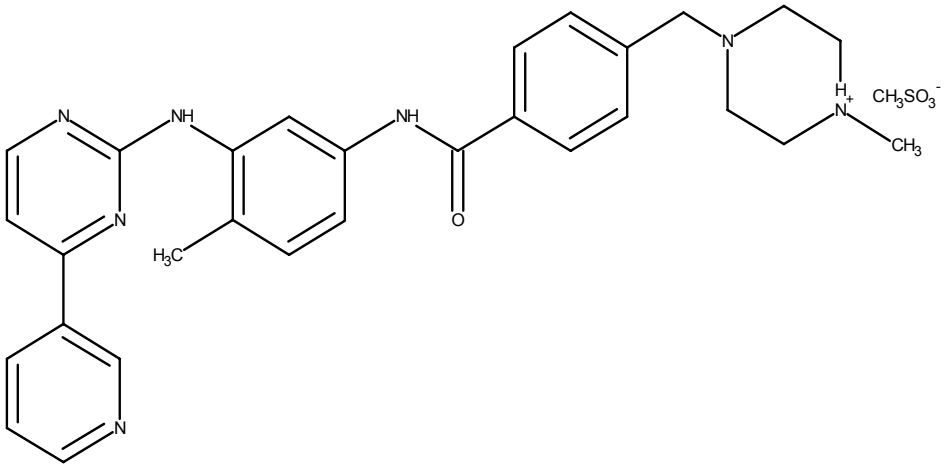

Fig. 1. Chemical structure of imatinib mesylate.

The title compound is know as inhibitor of tyrosine kinases and is indicated for the treatment of chronic myeloid leukemia, Philadelphia chromosome positive leukemia, for patients in chronic phase and in blast crisis, accelerated phase and also for malignant gastrointestinal stoma tumors. It selectivity inhibits activation of target proteins involved in cellular proliferation. Imatinib also has potential for the treatment of other cancers that express these kinases, including acute lymphocytic leukemia and certain solid tumors.

The main aim of presented study was to test the influence of different aliphatic alcohols, used as solvents, on acquire polymorphic form of imatinib mesylate. To reach the goal, the α polymorph of the title compound was re-crystallized from different alcohols and the resulting product has been characterized using X-ray diffraction analysis, differential scanning calorymetry (DSC), and IR spectroscopy.

P-32

Potential Peptidic Urokinaze Inhibitors.

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Urokinase-type plasminogen activator (uPA), a trypsin like serine protease, plays an important role in several biological processes including tissue remodeling, cell migration and matrix degradation. The primary role of uPA is converse plasminogen into its active form plasmin, a broad spectrum serine protease, which parts in the fibrinolytic cascade. Overexpression of uPA has been found in various malignant tumours, especially in digestive system, respiratory system, bones, skin, breast, genital system, urinary system, brain and leukemia. High levels of urokinase are correlated with enhanced invasiveness, metastasis and poor prognosis.
Inhibition of plasminogen activation by uPA appears to be attractive approach for the therapy of tumour growth and metastasis. The P1 positive charged residue of a inhibitor (arginal, benzamidine and phenylguanidine) makes a salt bridge with Asp189 in the S1 pocket of uPA. In the other site S2 limited by His-57 residue of alanine is accommodated. When position P3 is occupied by unnatural D-amino acid and the side-chain projects into the S4 pocket. The site S4 of uPA contains His-99, and the residue of D-Ser could form a favorable interaction with this.
We present the synthesis of peptides of the general H-D-Ser-AA-Arg-OH formula (AA = Phe, Cha, Phg, Chg, Hphe, homoCha, α-MePhe, 1-aminocyklohexane) and its effect on the amidolytic activities of urokinase, thrombin, trypsin, plasmin, t-PA and kallikrein. The synthesized peptides were tested for hemolytic activity on pig's erythrocytes. We expected that the use of specific tripeptide sequence to urokinase would cause high urokinase selectivity [1, 2, 3]. The peptides were synthesized on the solid phase manually using standard Fmoc-based strategy.

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P-33

Physical Properties of Porphyrazines Possessing in the Core the Following Cations Mg^{2+}, Zn^{2+}, Cu^{2+}, Mn^{3+}, Fe^{3+}.

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Porphyrazines are aromatic macrocyclic compounds consisting of four pyrrolic rings linked together with azomethine groups instead of methine bridges found in porphyrins. The structure of the porphyrazine may be modified by introducing peripheral substituents at their β positions, as well as various metal ions to the central cavity. Both types of modifications significantly impact the UV-vis spectra. Paramagnetic ions (e.g. Cu^{2+}, Fe^{3+}) present in the macrocycle core significantly decrease singlet oxygen quantum yield generation, whereas diamagnetic ions (e.g. Zn^{2+}, Al^{3+}) retain photosensitizing properties [1].

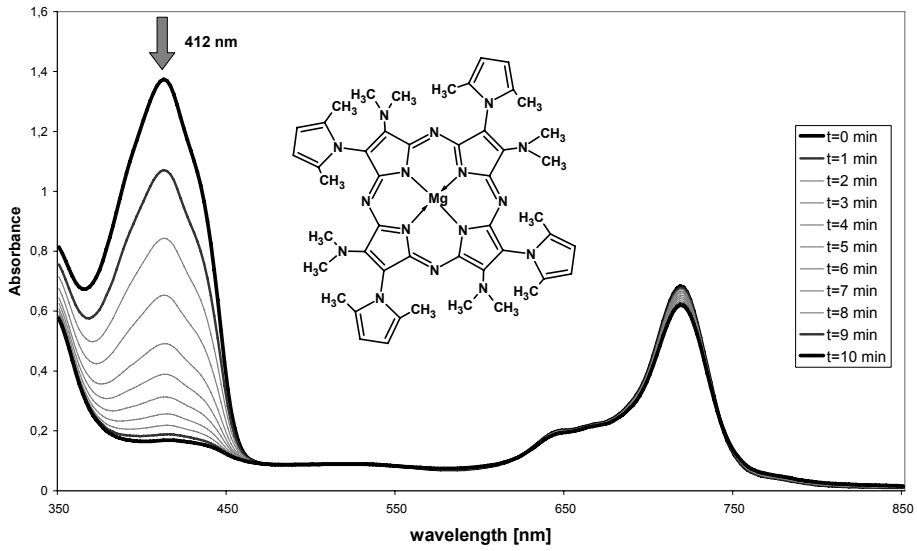

Fig. 1

Porphyrazines bearing mixed dimethylamino and 2,5-dimethylpyrrolyl groups in the periphery and Mg^{2+}, Zn^{2+}, Cu^{2+}, Mn^{3+}, Fe^{3+} metal ions in the core were investigated as singlet oxygen generators. 1,3-Diphenylisobenzofurane (DPBF) was utilized as a singlet oxygen quencher. DPBF-porphyrazine mixture was irradiated and the photodynamic reaction examined by UV-vis spectra (**Fig 1**). Significant decrease of DPBF quantity was observed for Mg^{2+} and Zn^{2+} porphyrazines, while in the case of other metals the changes found in the UV-vis profile are negligible. All porphyrazines were subjected to solvatochromic studies using various protic and aprotic solvents [2].

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This study was supported by STN grant from the University of Medical Sciences in Poznań, ”Synteza porfirazyn pochodnych metali bloku d o zastosowaniu w PDT i nanotechnologii”

P-34

Application of Highly Efficient Database Systems in Virtual Screening Protocol.

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Increasing power of modern multicore CPUs caused computational power to be raletively cheap nowadays and so processor time greed of Virtual Screening (VS) protocol is no longer an issue. However the amount of output produced and size of compound databases used for VS brought up new challenges, such as ways of sharing large amounts of data and flexible and rapid results analysis. In this poster we would like to introduce application of MySQL cluster database engine supporting results analysis and filtering.
Cluster database engine divides the data into smaller chunks and spreads them across the cluster nodes. This approach allows all the dataset to be held in RAM and so provides instant access to data and speeds up multitable querries by several magnitudes. In addition several applications were written for batch processing VS outputs and ease up visual inspection stage of virtual screening protocol.

Acknowledgements
This study was partly supported by a grant PNRF-103-AI-1/07 from Norway through the Norwegian Financial Mechanism.

P-35

Analysis of the Docking Process of Triazine Derivatives of the Nitrogen Iperite with Confirmed Antitumor Activity to the Binding Cavities of the Library of Artificial Receptors.

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The antitumor activity of nitrogen mustards (NM) has been associated with their ability to cross-link the twin strands of DNA, yielding bifunctional lesions, which if not repaired, can inhibit DNA replication and transcription, eventually leading to cell cycle arrest, apoptosis, and the inhibition of tumor growth. Since the alkylating ability of classical NM drugs do not operate selectivity, causing high levels of inadvertent DNA damage in normal cells, toxic and mutagenic side effects, the search is continued for NM derivatives with a modified structure, leading to more selectively acting analogues.

Recently, the new class of hybrid triazine derivatives of NM, active as anticancer agents, were obtained by selective functionalization of the triazine scaffold. In order to build a model for *in vitro* studies of the tissue distribution and stability of this new family of NM their docking into binding pockets of artificial receptors has been analyzed.

The library of 120 artificial receptors used in this studies were obtained by self-organization of N-lipidated dipeptides immobilized on cellulose support. Derivatives of NM were prepared from triazines substituted with alkoxy-, aryloxy-, alkylamino-, and amino-acid residues. Cytostatic activity on human breast adenocarcinoma cell line MCF7 was measured for all NM derivatives used.

The final goal of these studies was to select structural fragments of NM derivatives and of artificial receptors determining formation of the receptor-ligand binding complex and to design the model receptors library for *in vitro* screening activity of potential drugs.

P-36

The 1-[3-(4-Arylpiperazin-1-yl)propyl]pyrrolidin-2-one Derivatives as Antiarrhythmic Agents: a QSAR Studies.

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α_1-Adrenergic receptors (α_1-AR) are responsible for a number of physiological functions in:
(a) cardiovascular tissues regarding vascular smooth contraction and blood pressure regulation,
(b) noncardiovascular tissues regarding the human prostate smooth muscle contraction or the regulation of cerebral microcirculation.

Thus, α_1-AR antagonists can be useful in the treatment of hypertension, benign prostatic hyperplasia (BPH), lower urinary track symptoms (LUTS), or cardiac arrhythmia.

The existence of α_1-AR in the human heart has been proven using molecular biology, biochemical methods and functional studies. Cardiomyocytes of all mammalian species express all subtype of α_1-AR, even if their numbers represent only 25% to those of β-adrenoreceptors. However, in the failing human heart, there is a down regulation of β-AR while the number of α-AR is unchanged. Therefore, the more β-AR are reduced in serve heart failure, the more important α-AR mediated positively inotropic effect might become to maintain cardiac contractility. α_1-AR receptors play an important role in cardiac growth in the children and in the adult heart they inhibit the generation of atrial and ventricular arrhythmias.

Now, in the globalization era, determined by speed, uncertainty and instability people live in increasing stress leading to a rise in the incidence of cardiovascular diseases. Cardiac arrhythmia may be caused by abnormal impulse formation, abnormal impulse propagation, or both; it remains a major source of morbidity and mortality in developed countries. For example, between 0.5 and 1 million North Americans and Europeans die each year of sudden cardiac death, which corresponds to 10–20% of all deaths among adults in the Western world.

In the course of our studies directed to search for new α_1-AR antagonists, it was shown that the compounds obtained showed marked antiarrhythmic and hypertensive activities. The aim of the present study, being a part of our drug design project, is to find a model explaining the antiarrhythmic activity of a series of 1-[3-(4-arylpiperazin-1-yl)propyl]pyrrolidin-2-one derivatives applying the quantitative relationship between structural (QSAR) parameters and antiarrhythmic activity.

The activity of a number of 1-[3-(4-arylpiperazin-1-yl)propyl]pyrrolidin-2-one antiarrhythmic (AA) agents was described using QSAR model by applying it to 33 compounds. The molecular descriptors of the AA were obtained by quantum chemical calculations combined with molecular modeling calculations. The resulting model explains more than 90% of the variance and it was successfully validated by four tests (LOO, LMO, external test and Y-scrambling test). Statistical analysis shows that the AA activity of the studied compounds depends mainly on the PCR and JGI4 descriptors [1].

[1] Nowaczyk A., Przybylski R., Kulig, K.; Malawska, B.; *Mol. Inf.* 29 (4) (2010), 343.

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P-37

Synthesis and Photochemical Characteristics of Novel Norphthalocyanine Possessing Peripherally Annulated Perhydrodiazepine Ring.

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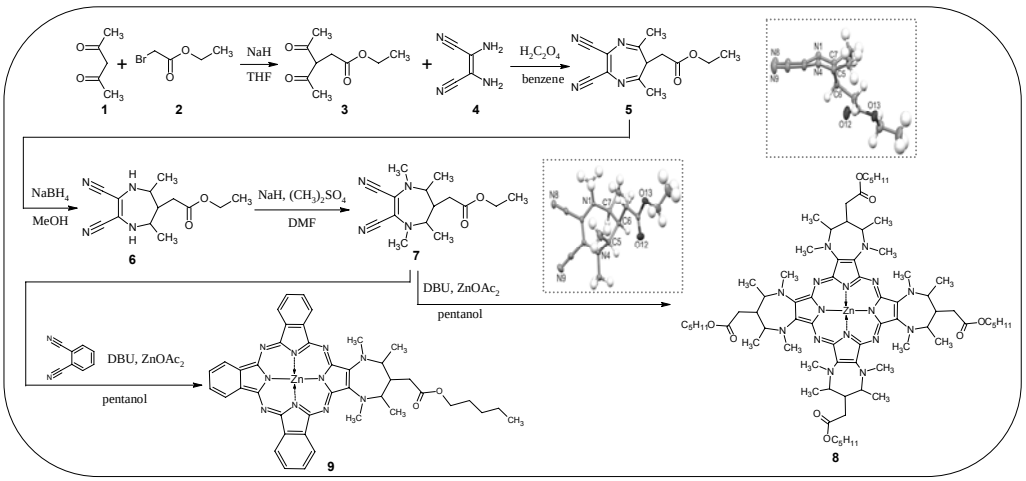
Seven-membered ring appended aminoporphyrazines have revealed very high singlet oxygen quantum yield generation. They could potentially be used as agents for photodiagnosis and photodynamic therapy [1]. The cellular uptake of photosensitizer involves binding to the cell membrane receptor and subsequent internalization. It may be affected by hydrophobicity and the aggregation status of the photosensitizer. The aim of our study was to functionalize the perhydrodiazepine ring with ester-alkyloxy substituents, which may help to encapsulate the macrocycle in some carriers, like liposomes, emulsions and nanoparticles.
New perhydrodiazepine porphyrazine (**8**) and norphthalocyanine (**9**) containing pentoxycarbonylmethyl group were synthesized (Figure). Alkylation reaction of acetylacetone (**1**) with ethyl bromoacetate (**2**) gave novel diketone containing ethoxycarbonylmethyl substituent (**3**). Subsequent condensation of **3** with diaminomaleonitrile (**4**) led to substituted diazepine (**5**). Its reduction with $NaBH_4$ gave perhydrodiazepine (**6**), which was subsequently methylated to perhydrodiazepine (**7**). Compound **7** was used in macrocyclization reaction with zinc acetate and DBU in pentanol in order to obtain novel symmetrical porphyrazine (**8**). Mixed macrocyclization of **7** and 1,2-dicyanobenzene using similar conditions gave novel light blue norphthalocyanine **9**. The structure of novel dinitriles **5** and **7** was confirmed by X-ray. Novel porphyrazine **8** and norphthalocyanine **9** were characterized using NMR and MS MALDI.



Solvatochromic effects in the range of protic and aprotic solvents, as well as singlet oxygen generation by new norphthalocyanine **9** were examined.

[1] Baum S., et al.: *J. Org. Chem.* 68 (2003), 1665.

This study was supported by the Polish Ministry of Science and Higher Education Grant No. N405 031 32/2052.

P-38

Design, Synthesis and Anticonvulsant Activity of New N–Mannich Bases Derived from 3-Phenyl-pyrrolidine-2,5-dione.

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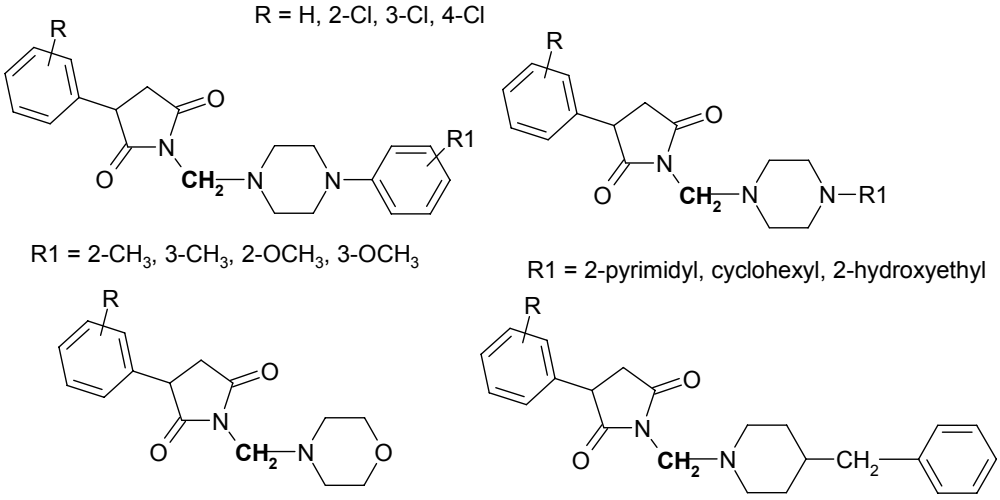
Recently we have shown that a great number of n-mannich bases derived from 3-phenyl-pyrrolidine-2,5-diones, containing at the imide nitrogen atom 4-arylpiperazines with electron-withdrawing substituents, exhibited anticonvulsant activity, especially in the maximal electroshock (mes) test [1-3]. Carrying on our research, in the present work we synthesized several analogues, of compounds mentioned above, containing at position-3 of the pyrrolidine-2,5-dione aromatic ring with the chloro atom at position *ortho, meta* or *para.* On the other hand, we introduced at the aromatic ring of piperazine the electron-donating substituents, such as methyl- or methoxy- groups. Finally, we changed 4-arylpiperazines to pirymidyl-, cyclohexyl- and 2-hydroxyethyl-piperazines, as well as, in place of these amines we introduced benzylpiperidine or morpholine moieties. The structures of targeted compounds are presented below.



All the compounds were evaluated for their anticonvulsant properties through the Antiepileptic Drug Development (ADD) Program, by testing procedures, which have been described elsewhere [4].

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[4] Kupferberg H.J.: *Epilepsia* 30 (suppl.) (1989), 51.

P-39

Evidence for Polymorphism of Zolendronic Acid Monohydrate.

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Polymorphs are defined as different arrangement and/or conformations of the molecules within the crystal lattice [1]. The investigation of the drug polymorphism is crucial because it may have a considerably influence on solid state physical properties which can alter the biopharmaceutical behavior of the drug. Bisphosphonates such as zolendronate are an important class of drug molecules that are currently widespread used to treat a variety of bone resorption diseases [2] .
It has also been found that they have considerable in vitro activity against a variety of trypanosomatid parasites, including *L.donovani*, *Trypanosoma cruzi*, and *Trypanosoma brucei* [3] as they are potent inhibitors of farnesyl pyrophosphate synthase [4]. Bisphosponates have also been find to stimulate $\chi\,\delta\,\Upsilon$ cells of the immune system [5], this can be of interest in the context of cancer immunotherapy.
In this study, the polymorphism of zolendronic acid monohydrate (Fig. 1) has been investigated. Three polymorphs have been prepared by recrystallization from water in different conditions. The different solid form of zolendronic acid monohydrate have been characterized using X-ray diffraction analysis, differential scanning calorymetry (DSC), thermogravimetric analysis (TG), IR spectroscopy and optical microscopy.

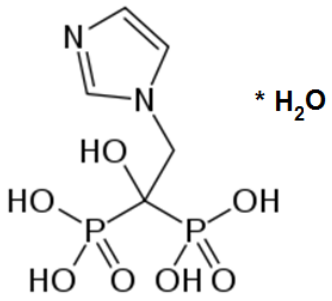

Fig.1. Chemical structure of zolendronic acid monohydrate.

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[4] Sanders J. M., Ghosh S,, Chan J. M., Meints G., Wang H., Raker A. M., Song Y., Colantino A., Burzynska A., Kafarski P., Morita C. T., Oldfield E.: *J. Med. Chem.* 47 (2004), 375.
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P-40

Structure Determination of Novel Porphyrazines Possessing Peripheral 2,5-Dimethylpyrrolyl and Dimethylamino Groups Using Computational Methods and Infrared - Raman Spectroscopy.

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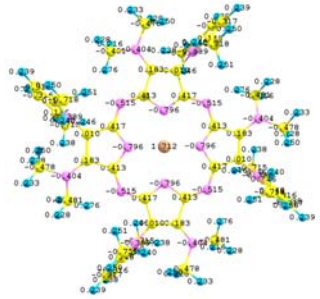
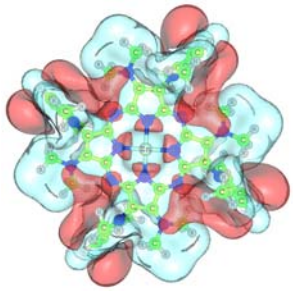
Porphyrazines are very promising group of photosensitizers widely studied in many laboratories all over the world. These compounds have revealed potential applications in photodynamic therapy, nanotechnology and biomimetics. The new series of porphyrazines, the free base 2,7,12,17-tetrakis(dimethyloamino)-3,8,13,18-tetrakis(2,5-dimethyl-1*H*-pyrrol-1-yl)porphyrazine and its complexes with Mg(II), Zn(II), Cu(II), Fe(III) and Mn(III), were examined for its near infrared absorption, Raman spectra and molecular modeling studies.

Applied computational model was based on Density Functional Theory B3LYP correlation-exchange potential and basic functions 6-31G(d,p) implemented in the Firefly [1] program. Optimized molecular geometry showed for all compounds C4 symmetry except free base (C2) which corresponds with crystallographic data. Molecular parameters such as dipole moment, energy of molecular orbitals, HOMO-LUMO energy gap, Mulliken and Natural Bond Orbital population analysis, electrostatic potential and electrostatic density were determined. Simulation of infrared spectra was performed for gas phase, with the same B3LYP/6-31G(d,p) model.

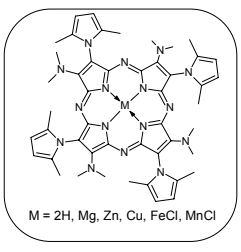
Most characteristic bands present in experimental infrared absorption and Raman spectra were compared to simulated and literature values [2,3]. Bands representing aromatic pyrrole stretching ν_{sym}C-H and pyrrole methyl group ν_{asym} and ν_{sym} C-H were observed between 3099-3101 cm^{-1}, 2915-2924 cm^{-1} and 2854-2859 cm^{-1}, respectively. Strongly shifted dimethylamino group vibrations ν_{sym} C-H were observed in the range 2798-2806 cm^{-1}. The pyrrole ring stretching νC=C, two bending in plane β_{sym}C-H and bending out of plane γ_{sym}C-H vibrations were observed between 1589-1600 cm^{-1}, 1054-1075cm^{-1}, 1013-1015 cm^{-1} and 746-752 cm^{-1}, respectively. Dimethylamino group showed strong vibrations for umbrella asymmetrical bending δ_{asym}C-H (1402-1409 cm^{-1}), symmetrical umbrella bending δ_{sym}C-H (1375-1380 cm^{-1}) and typical for tertiary amines νC-N (1310-1323 cm^{-1}). Free base revealed stretching vibrations ν_{sym}N-H at 3292 cm^{-1}. The differences observed between simulated and experimental frequencies of the most representatives bands were less than 3%.



1. Charge distribution. Natural Bond Orbital Theory analysis for Zn derivative



2. Electrostatic potential for Zn derivative (Isosurface 0.01 a.u., light negative, dark positive values)



3.Structures of new porphyrazines

[1] Granovsky A. A.: Firefly version 7.1.G, www http://classic.chem.msu.su/gran/firefly/index.html. [2] Katritzky A. R., Rees C. W.: *Comprehensive Heterocycle Chemistry*, Pergamon Press, Oxford, **1984**, vol. 4. [3] J. Coates, *Interpretation of Infrared Spectra, A Practical Approach*, in *Encyclopedia of Analytical Chemistry,* John Wiley & Sons Ltd, Chichester, 2000.

This study was supported by STN grant from the University of Medical Sciences in Poznań, SBN 502-05-03313427-50528.

P-41

Molecular Docking Study of Stereoisomers of Fenoterol Derivatives to the β_2 Adrenergic Receptor and Molecular Dynamics Simulations for the Selected Agonist-β_2-AR Complexes.

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[b] *Institute of Catalysis and Surface Chemistry, Polish Academy of Sciences, Kraków*
[c] *Laboratory of Clinical Investigations, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA*
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The β_2 adrenergic receptor (β_2-AR) has become a model system for studying the ligand recognition process and mechanism of GPCR activation. In the present study we use stereoisomers of fenoterol and some of its derivatives as a molecular probe to identify differences in stereo-recognition of structurally similar agonists. Fenoterol (Fig.1) is a selective β_2-AR agonist existing as four stereoisomers which significantly differ in β_2-AR binding affinities and selectivities. The clinically used drug, *rac*-fenoterol, is a racemic mixture of (R,R)-fenoterol and (S,S)-fenoterol, used for the treatment of asthma. Fenoterol stereoisomers and derivatives were docked to the molecular model of β_2-AR, based on the crystal structure of β_2-AR, cocrystalized with an inverse agonist – carazolol (PDB 2RH1) [1]. In particular, docking studies were applied to the set of fenoterol derivatives (n = 32), in case of which the enantioselectivity plays a crucial role. The stereoisomers of fenoterol were docked into one binding site using several docking procedures by using the Molegro Virtual Docker (MVD) software. Agonist molecules occupy the same binding region, located between TM3, TM4, TM5, TM 6 and TM7. The following residues identified by us during docking procedure were experimentally indicated in functional and biophysical studies as being very important for the formation of the hydrogen bonds: Asp113, Ser204, Ser207, Asp192, Asp191, Asn293, Tyr308. Correlations between the function score values and the compound binding affinities (the latter expressed as the K_i values) were examined. According to our study, docking in MVD offers a good prediction of the binding energies (expressed as the scoring function values). In addition, molecular dynamics (MD) simulations of obtained complexes were carried out (GROMACS 3.3 package and GROMOS96 53a6 force field). These simulations gave us better insight into receptor-ligand interactions and system evolution in time. Furthermore, the LIE (Linear Interaction Energy) method was used to calculate the binding free energy (ΔG) for stereoisomers of fenoterol by averaging interaction energies obtained from MD simulations. The results of this latter study show very different thermodynamic characteristics of binding to β_2-AR, dependent on the stereoconfiguration of the ligand. The theoretical results obtained by us are in agreement with the experimental data [3].

Both the experimental and theoretical data demonstrate that the stereochemistry of the fenoterol molecule influences the magnitude of binding affinity, the thermodynamics of local interaction of ligand within the binding site of β_2-AR [2, 3].

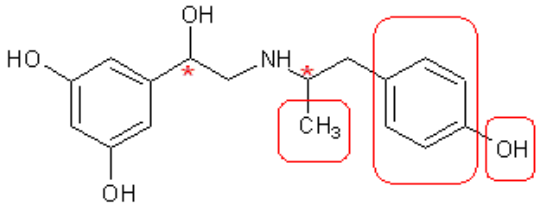

Fig. 1. The structure of (R,R)-fenoterol in which the sites of the molecule probed in this study are circled in red.

[1] Cherezov V., *et al.*: *Science* 318 (5854) (2007), 1258.
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P-42

New Strategy for Use of Pharmacophore Models in Virtual Screening for 5-HT$_6$ Receptor Ligands.

Katarzyna Prymula [a,b,c], *Tomasz Kościółek* [a], *Rafał Kurczab* [a], *Stefan Mordalski* [a], *Grzegorz Satała* [a], *Dawid Warszycki* [a], *Andrzej J. Bojarski* [b]

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Receptors of 5-hydroxytryptamine subtype 6 (5-HT$_6$) are almost exclusively expressed in brain, therefore constitute a good therapeutic target related to central nervous system (CNS) diseases. Indeed they are implicated in many CNS disorders including cognition and memory disorders [1]. As a result, the interest in discovery of novel 5-HT6 receptor ligands is high nowadays which can be illustrated by molecular diversity of active templates [2,3]. Concurrently, there is a need for elucidation of the mode by which ligands bind at the receptor site. The latter issue caused some controversy and is still unsolved. The right solution to those two problems may be given by pharmacophore models.
Firstly, based on data from patents and publications, a database of compounds tested *in vitro* against 5-HT$_6$ receptors was created. Next, 5-HT$_6$ ligands were clustered using molecular fingerprints (MOLPRINT2D method implemented in Canvas, Schrödinger), and ligand-based pharmacophore hypotheses were generated (HipHop/Catalyst, Accelrys). The obtained common feature pharmacophore models were clustered and validated on a test set containing active and inactive compounds. The best hypotheses were checked for consistency with known ligand structure-activity relationships (SARs) and structural characteristics recognized for binding. Hypotheses were further extended by adding excluded volumes. Finally we performed the virtual screening of two commercially available databases using set of developed pharmacophore models assuming that such diversity of 5-HT$_6$ ligands may results in more than one binding mode. This strategy has not been used previously in search for 5-HT$_6$ ligands, even though there are evidences for second binding mode of 5-HT$_6$ antagonists [4].

Acknowledgements
This study is supported by project UDA-POIG.01.03.01-12-063/09-00 "Antagonists of 5-HT$_6$ receptor as advanced antipsychotic drugs with pro-cognitive properties" co-financed by European Union from the European Fund of Regional Development (EFRD).

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P-43

ADBO: Source of New Cytostatics.

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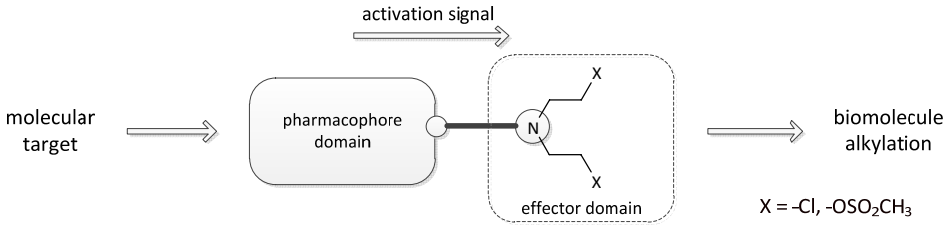
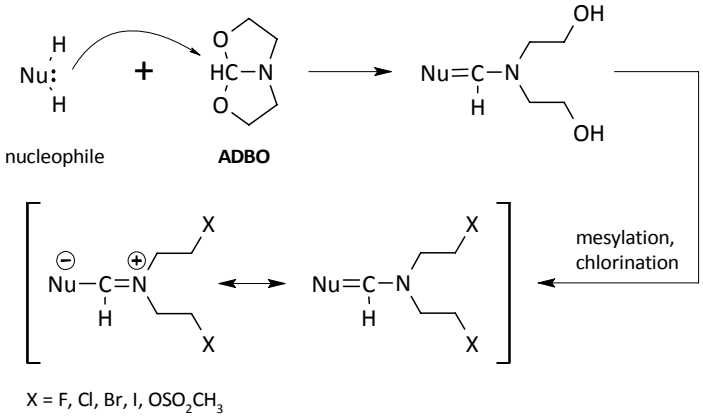
Our research are focused on a methodology for synthesis of new antitumor-active compounds, whose chemical structures consist of two domains responsible for interacting with the cellular target and generation of pharmacological response. The structural changes in the pharmacophore part caused by its enzymatic interaction with the tumor specific biomolecule activate the latent effector domain and lead to cell destruction. The bis(2-chloroethyl)amine (nitrogen mustard) moiety is chosen as a universal effector unit due to its strong, non-specific and proportional to dose cytotoxicity [1] even against mitotic inactive cells [2].



An efficient and versatile route for the preparation of new substances, through incorporation of nitrogen mustard moiety into the structure of different molecules with ability to selective interaction with some molecular targets, is possible by the reactivity of the amidoacetal named 1-aza-4,6-dioxabicyclo[3.3.0]octane or ADBO [3]. One-pot reaction of nucleophiles having at least two protons with ADBO followed by chlorination or mesylation of obtained products leads to desired compounds characterized by strong but latent pharmacological activity [4] (Rozanski, 2001).



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P-44

Photochemical Assessment of Pyrrole Porphyrazines as Potential PDT Agents.

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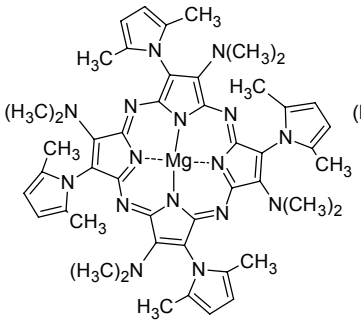

TG-WS-II-28A MM091118

Photodynamic therapy (PDT) is promising new treatment mainly cancer, pre-cancer changes, bacterial and virus infection. In PDT is used three components such as photosensitizer, molecular oxygen and light of an appropriate wavelength. This three agents aren't active separately but together lead to cell death. Upon absorption of appropriate wavelength light, the excited stage of the photosensitizer is formed. Excited form of the drug reacts with a molecular oxygen yielding singlet oxygen. Singlet oxygen can react with many biological components of cell or tissue and cause their destruction. For selective treatment after drug injection only pathologic tissue is irradiated.

The photochemical properties of two porphyrazines (TG-WS-28A and MM091118) were studied in order to evaluate their potential usefulness in photodynamic therapy. The compounds were synthesized in the Department of Chemical Technology of Drugs, Faculty of Pharmacy (Poznan University of Medical Sciences). The porphyrazines are metallated in the core with Mg(II) – TG-WS-II-28A or Zn(II) – MM091118 ions. The photodegradation and singlet oxygen generation were studied.

The photodegradation of porphyrazines were performed in three solvents – dimethylformamide (DMF), dimethylsulfoxide (DMSO), tetrahydrofuran (THF). Both compound were found photounstable. The progress of photodegradation was different for TG-WS-II-28A and MM091118. The time of this process was also depended on solvent. The photochemical stability of TG-WS-II-28A was found to be greater than that of MM091118. Quantitative evaluation of photostability was performed on the basis of photodegradation kinetic parameters. Photodegradation appeared to follow in two stages first-order kinetics.

Singlet oxygen generation is the basis for further research into the potential use of these compounds in PDT. The singlet oxygen generation by TG-WS-II-28A and MM091118 were studied. 1,3-Diphenyloisobenzofuran (DPBF) was used as a singlet oxygen quencher. The photooxidaction process was investigated in aerobic conditions and in environment with limited access of oxygen. The result showed that both porphyrazines generate singlet oxygen, but in environment with limited access of oxygen this process occurs to a much lesser extent. The quantum yield of singlet oxygen generation was estimated by comparing with zinc phthalocyanine (ZnPc), used as a standard. The evaluation showed that MM091118 is the most efficient photosensitizer. The quantum yield of singlet oxygen generation was for TG-WS-II-28A 0,27 and 0,28, for MM09118 0,37 and 0,52 in DMF and DMSO, respectively.

P-45

Synthesis and Biological Evaluation of *trans*-Methylthiostilbene Derivatives – Potential Chemopreventive and Chemiotherapeutic Agents.

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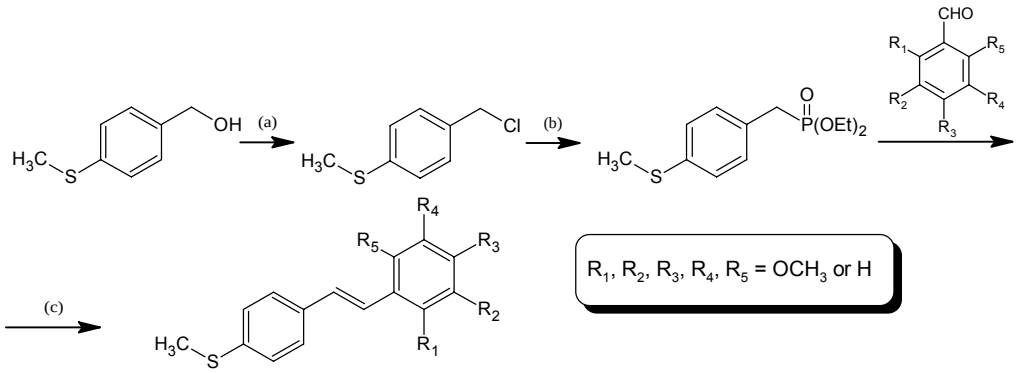
Interest in the concept and practice of chemoprevention as an approach to the control of cancer has increased greatly in the past few years especially due to the unsatisfactory results of classic chemotherapy. Many agents among which stilbenes: the most representative, resveratrol (RSV) (3,4',5–trihydroxy-*trans*-stilbene) and its naturally occurring methoxy derivatives like pterostilbene (4'–hydroxy–3,5–dimethoxy-*trans*-stilbene) have been shown to be effective for blocking carcinogenesis in certain human cancer and animal models. *In vitro* mechanisms of action of RSV have been extensively discussed in numerous reports and reviews. Several key mechanisms of action include: inhibition of the transcription factor NF-κB, regulation of cytochrome P450 enzymes, activation of nuclear receptors such as estrogen receptors (ERs), inhibition of expression and activity of inflammation-related enzymes such as cyclooxygenases and regulation of sirtuins. These facts lead to the conclusion that RSV might be the potential lead structure for cancer chemopreventive and chemotherapeutic compounds.
Our previous studies have been shown that a series of 4'-methylthio-*trans*-stilbene derivatives differing in a number and position of additional methoxy groups exhibited high affinity toward active sites of CYP1 enzymes involved in the activation of procarcinogens, in particular CYP1A1 and CYP1B1 [1].



Scheme 1. General synthetic route for synthesis of the *trans*-methylthiostilbenes analogues.
Reagents and conditions: (a) $SOCl_2$, toluene, rt.; (b) $P(OEt)_3$, 130°C;
(c) NaH, DMF, rt.

In the present work we have synthesized a series of *trans*-methylthiostilbene derivatives and investigated the cytotoxic activity towards human breast cancer MCF-7 cell line and their effect on NF-κB activation. The corresponding *trans*-methylthiostilbenes were prepared using standard chemical methodologies. The obtained results showed that compounds possessing three methoxy residues, 2,3,4- and 2,4,5-trimethoxy-4'-methylthio-*trans*-stilbene have the strongest antiproliferative potential in MCF-7 cells. No significant effect on NF-κB activation has been observed.

[1] Mikstacka R., Baer-Dubowska W., Wieczorek M., Sobiak S.: *Mol. Nutr. Food Res.* 52 (2008), S77.

This study was partially supported by grant from the Poznań University of Medical Sciences, 501-02-03313427-06990-50552.

P-46

Synthesis of New 1-(1-Arylimidazolidyn-2-ylideno)-3-aminosulfonylurea.

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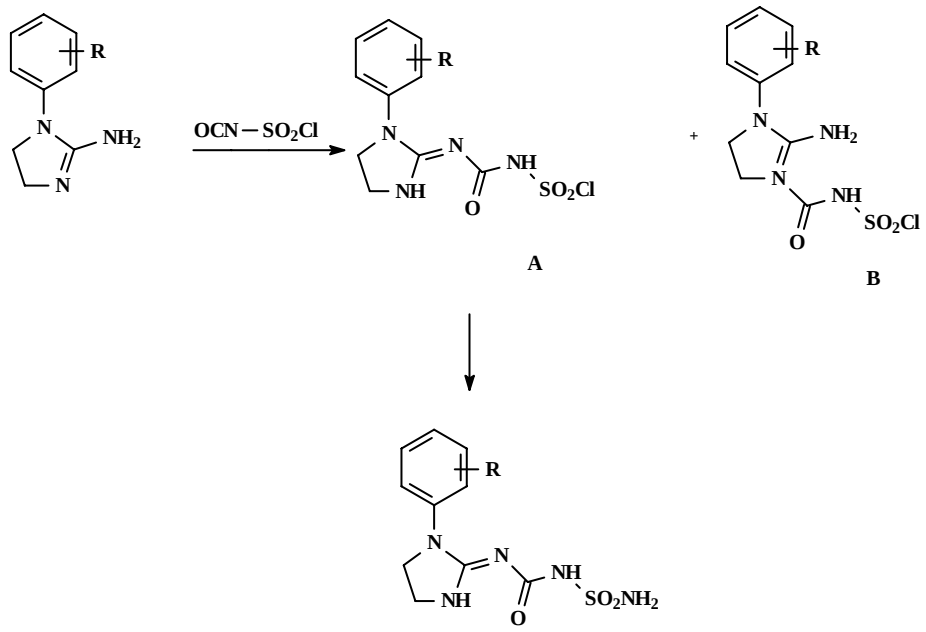
1-Aryl-2-aminoimidazoline were used to synthesize many chain and fused imidazoline derivatives exhibiting pharmacological activity. Compounds bearing the 1-aryl substituted were found to process significant central activity, especially antinociceptive and serotonergic.[1-3]. In the search for new derivatives with potential pharmacological activity received of new 1-(1-arylimidazolidyn-2-ylideno)-3-aminosulfonylureas.

Scheme :



The structure of all new compounds was confirmed by elementar analysis, as well by the ^{1}H NMR.

[1] Matosiuk D., Fidecka S., Antkiewicz-Michaluk L., Dybała I., Kozioł A.E.: *Eur. J. Med.. Chem.* 36 (2001), 783.
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P-47

Crystal Structures of Aryldithiocarbazonics Showing Tuberculostatic Activity.

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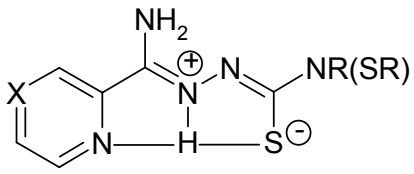
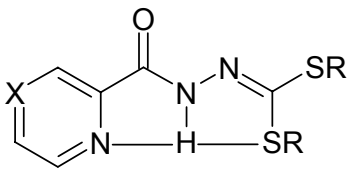
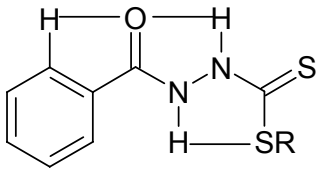
Increasing resistance of *Mycobacterium tuberculosis* against existing agents and resulting spread of the pathogen also in developed countries made a search for new tuberculostatics an important issue.
Our studies on crystal structures of tuberculostatics having general formula **1** revealed a bifurcated intramolecular hydrogen bond between the protonated N atom as a donor and two acceptors (anionic S atom and N atom at *ortho* position of the ring) [1-3]. As a result the molecules are planar, which also cooperates with the conjugation of π-electron systems present in these structures.
Replacement of amino group to carbonyl one (**2**) enables formation of similar hydrogen bonds that favors planarity, which has been suggested as a prerequisite for tuberculostatic activity [2].
Thus we were surprised to find out that the activity is maintained in case of type **3** compounds (replacement heteroaryl to phenyl), which has no acceptor function and can not participate in the same itramolecular hydrogen bond. However, in this case planarity is promoted by other intramolecular attractive interactions.
Thus our working hypothesis helpful in further search for active benzoilodithiocarbazonic derivatives is as follow: "planarity of a molecular fragment spread between dithiol and aryl groups (inclusive) is a prerequisite for tuberculostatic activity in the studied compounds".



1



2



3

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P-48

Synthesis and Structure of Urea Derivatives of Hydantoin.

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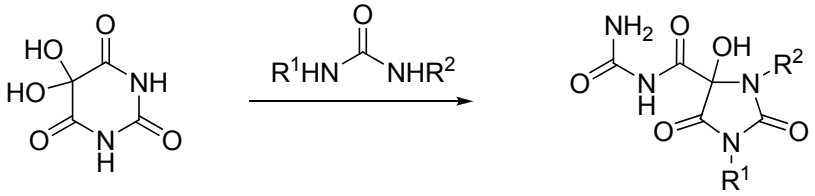
Compounds based on the imidazolidine-4-one scaffold such as hydantoin, 2-thiohydantoin and creatinine analogs show a wide range of biological activity including their anticonvulsant, antiarrhythmic, antihypertensive, antibacterial or fungicidal properties. Due to biological importance of this class of compounds, their molecular structure has been a target for numerous spectroscopic and crystallographic studies. Phenomenons of tautomerism and stereoisomerism observed among this class of compounds, as well as various motifs of multiple hydrogen bonded network, seen in the crystals of derivatives of imidazolidine-4-one, have been studied intensively also in our group [1-3].
At the present work we report synthesis, spectroscopic properties and crystal structures of a series of hydantoin analogs, products of the reaction of alloxan with urea and its alkyl and dialkyl derivatives.



1

2 $R^1 = R^2 = H$
3 $R^1 = Me$; $R^2 = H$
4 $R^1 = Et$; $R^2 = H$
5 $R^1 = R^2 = Me$
6 $R^1 = R^2 = Et$

[1] Książek W., Kieć-Kononowicz K., Karolak-Wojciechowska J.: *J. Mol. Struct*. 921 (2009), 109.
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This work was partly supported by Polish Ministry of Science and Higher Education, Grant Nr N N405 184635.

P-49

Computational Modeling of Interactions Between Nicotinic Acetylcholine Receptor and Different Classes of Allosteric Modulators.

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Nicotinic acetylcholine receptor (nAChR) is an archetypical member of the Cys-loop Ligand Gated Ion Channels superfamily. It is an pentameric assembly of separate membrane subunits oriented around a centrally located pore permeable of cations. Several neuronal subtypes of nAChR pose a promising target for treatment of such disorders as nicotine addiction, depression, schizophrenia, cognition deficits and treatment of pain. A large number of marketed drugs and their metabolites interact with the channel domain and modulate negatively the receptor activity by a mechanism of non-competitive inhibition associated with physical blocking of the actual ion channel. The allosteric positive modulators interact with outer and inner surface of the extracellular domain (ECD) of nAChR. Binding of allosteric ligand molecules plays important roles in coupling agonist binding to the channel gating.
In our studies we developed a panel of interdisciplinary methods to characterize interactions of several classes of medicinal compounds with different subtypes of the receptor. We performed two sets of molecular modeling simulations for two distinct part of nAChR and its interactions with ligand molecules. Models of 1) the ion channel domain and 2) the extracellular domain (ECD) were developed for several subtypes of the receptor and were used in docking simulations of ligands interacting at these locations. In project 1) the molecular model of transmembrane domain of the nAChR obtained using cryoelectron microscopy of *Torpedo marmorata* (PDB id: 2BG9) was used. We further modified this model to represent models of the several human neuronal and muscular subtypes. Docking procedures of a flexible ligand into the rigid model of the ion channel were performed and allowed classification of ligands in respect to their binding energies. Obtained result for the interactions with ion channel indicated that ligands stably interact with the surface of the channel formed by an assembly of five transmembrane helices M2. The binding energy estimated in simulations can be related to experimental values [1,3]. In project 2) the molecular models of extracellular domain of nAChR obtained from *Lymnaea stagnalis* (PDB id: 1UV6) and *Gloeobacter violaceus* (PDB id: 3EAM) were used. We constructed the models representing different neuronal subtypes of ECD of nAChR using homology modeling. Obtained models were used for docking simulations of such ligands as galanthamine, physostygmine, 5-hydroxytryptamine [2], ketamine and its metabolites. Obtained results suggest that allosteric potential ligands bind to different locations than acetylcholine and affect the function of the receptor. Our study elucidates how computational molecular modeling can be used to support modern research in pharmacology and medicinal chemistry.

[1] Arias H. R., et al.: *Int. J. Biochem. Cell. Biol*. 42 (2010), 1007.
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[3] Arias H. R., et al.: *Int. J. Biochem. Cell. Biol.* 42 (2010), 1525.

P-50

Synthesis of Fluorinated Aryloxypropanol Analogues as Potential Adrenoreceptore Blocking Agents.

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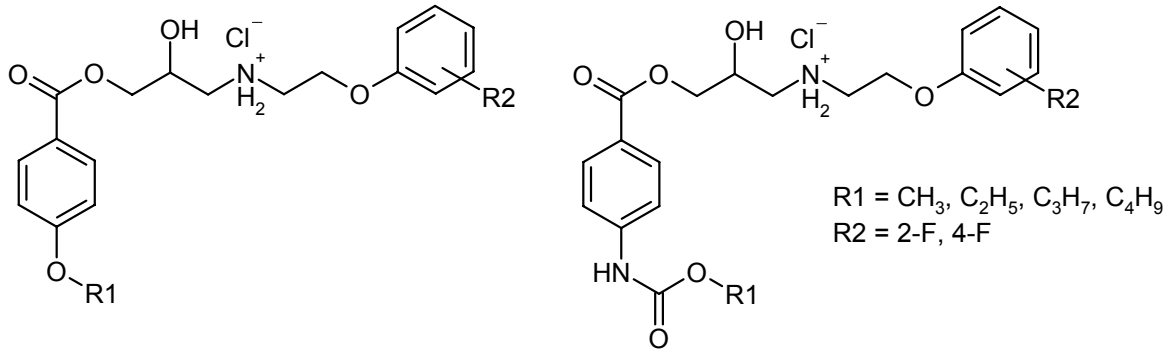
e-mail: tenglerj@vfu.cz

Aryloxyaminopropanols containing phenoxyethylamine moiety in their molecule usually show alpha-adrenolytic activity as well as the beta–adrenolytic one (e.g. carvedilol). The aim of this project was to prepare a series of novel aryloxyaminopropanol analogues substituted by phenoxyethylamine fragment fluorinated in ortho or para position. Introduction of fluorine atom promises similar effect as introduction of methoxy group [1]. Final products were obtained by multiple- step synthesis starting from 4-alkoxybenzoic or 4-[(alkoxycarbonyl)amino]benzoic acid. Lipofilicity of these compounds was affected by different length of alkyle group (R1). Presence of ester bond could be responsible for reduction of biological half-life.



R1 = CH_3, C_2H_5, C_3H_7, C_4H_9
R2 = 2-F, 4-F

Main physical and chemical properties of these compounds were evaluated. Acid-base dissociation konstant, *pKa*, was determined by ^{1}H NMR spectroscopy and CZE. Acquired values were compared with methoxy derivates prepared previously.

[1] Fumagalli L., et al.: *Bioorg. Med. Chem.* 13 (2005), 2547.

This work was supported by grant of University of Veterinary and Pharmaceutical Sciences Brno, *IGA VFU Brno No. 23/2010/FaF*

P-51

Preparation of 3-Alkylamino-2-Hydroxypropyl-4-(2-Alkoxyethoxy) Benzoates.

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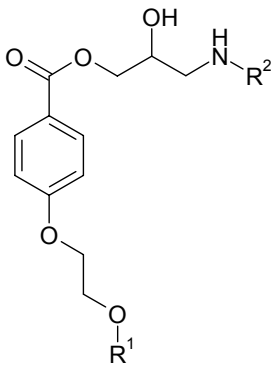
Most of beta-blockers in clinical use belong to group of aryloxyaminopropanol derivatives. The purpose of this work was to prepare a new set of arylcarbonyloxyaminopropanol analogues with potential beta-adrenolytic effect to follow on structure-activity relationships studies proceeding at our department. Final compounds have ether group replaced by metabolically labile ester bond to reduce a biological half-life, aromatic ring is substituted in para position by alkoxyethoxy group to increase cardioselectivity. Multiple-step synthesis of final products starting from 4-hydroxybenzoic acid is described. Their structure and purity was confirmed by ^{1}H-NMR, ^{13}C-NMR, IR spectroscopy and TLC. Synthesis of separate enantiomers using chiral precursors *R*-(+)- and *S*-(-)-2,3-epoxypropanols carries out currently. Enantiomeric purity of optically active intermediates and products was evaluated by NMR spectroscopy using the lanthanide shift reagents ($Pr(hfc)_3$, $Eu(hfc)_3$).



R^1 = $-CH_3$, $-CH_2CH_3$
R^2 = $-CH(CH_3)_2$, $-C(CH_3)_3$

This work was supported by grant of University of Veterinary and Pharmaceutical Sciences Brno, *IGA VFU Brno No. 23/2010/FaF*

P-52

Microbiological *Cunninghamella* Model for Metabolism Assay of Antiepileptic Drug Candidates.

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Compounds KM113 and KM314 have undergone a series of pharmacological tests in mid-preclinical phase and are considered new antiepileptic drug candidates. Both compounds proved effective in many in vivo models, including 6 Hz test and a lamotrigine model of drug resistant epilepsy. Moreover, both KM113 and KM314 underwent *in silico* simulation of metabolism [1] and were tested *in vitro* on human P_{450} isozymes for possible induction or inhibition [2].
Therefore, potential ability of microorganism *Cunninghamella* [3] to carry out the biotransformation of these two compounds and their enantiomeric and racemic forms was tested. Biotransformation of KM113 and KM314 was carried out using three strains of filamentous fungus: *Cunninghamella echinulata* NRRL 1384 [4], *Cunninghamella elegans* DMS 1908 [5], *Cunninghamella blakesleeana* DMS 1906 and a bacterial strain - *Lactobacillus kefiri* DMS 20587. Compounds which were introduced into the culture were dissolved in a mixture of water and organic solvent (DMSO). The use of co-solvent was dictated by poor solubility of the substances in water. Only the strain *Cunninghamella echinulata* 1908 DMS 20587 was able to carry out the biotransformation of only KM314 and its enantiomers. The process of biotransformation proved to be inefficient, so that it was impossible to isolate derived metabolites and determine their structures.

Acknowledgements:
The authors would like to thank prof. James P. Stables from National Institute of Neurological Disorders and Stroke, NIH, Rockville, USA for providing pharmacological results.
The Project is supported by the European Regional Development Fund through the Innovative Economy Program.

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P-53

The Influence of Aromatic Substituent in Position 6 of 4-(4-Methylpiperazin-1-yl)-1,3,5-Triazin-2-Amine Derivatives on Histamine H_4 Receptor Affinity.

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[a] *Department of Technology and Biotechnology of Drugs, Faculty of Pharmacy, JagiellonianUniversity Medical College, Medyczna 9, 30-688 Kraków*
[b] *Institute of General and Ecological Chemistry, Technical University of Łódź, Żeromskiego 116, 90-924 Łódź*
[c] *Institute of Pharmaceutical Chemistry, Johann Wolfgang Goethe University, Max-von-Laue Str. 9, 60438 Frankfurt, Germany*
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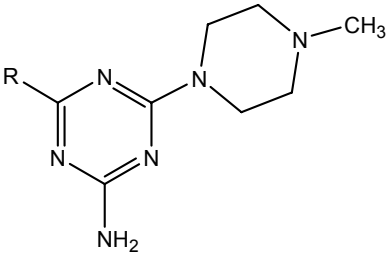
The histamine H_4 receptor (H_4R) is the latest identified receptor belonging to the histamine receptor family. This receptor is preferentially expressed on hematopoietic and immune cells (basophils, eosinophils, mast cells, macrophages), suggesting a role in immunological and inflammatory processes [1]. Recently Connelly *et al.* described that the H_4R is also present in the central nervous system (CNS) as a post-synaptic receptor [2]. JNJ 7777120 (indole carboxamide derivative) is the first potent and selective H_4R antagonist used as reference compound to study the H_4R [3]. Many pharmaceutical companies and academic research groups have synthesized a large variety of high potent H_4R ligands [3,4].

The aim of this work was the search for H_4R ligands in the group of 4-(4-methylpiperazin-1-yl)-1,3,5-triazin-2-amine derivatives (Fig 1).



The series of 4-(4-methylpiperazin-1-yl)-1,3,5-triazin-2-amine derivatives with different aromatic substituents in 6-position was synthesized. X-ray structure analysis was performed for representative triazines. Compounds were tested for the human H_4R affinity. H_4R binding assay was performed on *Sf*9 cells expressing human H_4R co-expressed with G-protein $G\alpha_{i2}$ and $G\beta_1\gamma_2$ subunits. Non-specific binding was determined in the presence of 100 μM unlabelled histamine [5]. The compounds have shown H_4R affinities with K_i values in the (sub)micromolar concentration range.

Fig 1.

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P-54

Determination of the Lipophilicity of Arylpiperazynylalkyl Derivatives of Imidazo[2,1-f]Theophylline by RP HPLC.

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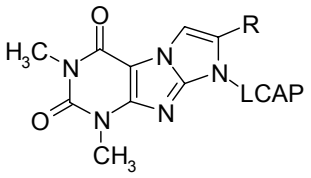
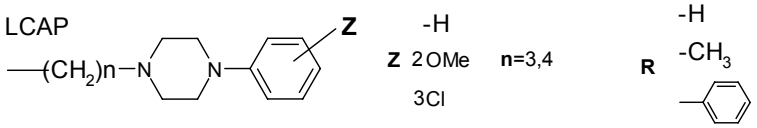
The arylpiperazines with an amide moiety are one of the most frequently investigated classes of 5-HT_{1A}/5-HT_{2A} receptor ligands. Although the terminal amide fragment significantly affects binding of 1-arylpiperazine derivatives for serotonin receptors, its role is not clear yet [1]. In our earlier attempt to find new 5-HT_{1A}/5-HT_{2A} receptor ligands, a series of the imidazo[2,1-f]theophylline derivatives with the arylpiperazinylalkyl substituent at N8 position had been synthesized. These compounds have been tested in vitro for their 5-HT_{1A} and 5-HT_{2A} ,receptor affinities and were potent 5-HT_{1A} receptor ligands with K_i within the range on 5,6-96,5nM and demonstrate lack of affinity for 5-HT_{2A} subtype [2].





Lipophilicity as a physicochemical factor is particularly crucial for compounds with potential CNS activity therefore it is often used in quantitative structure-activity relationship studies [3]. Lipophilicity can be determined by classic method of determination of partition between water and n-octanol to most recently, the use of reversed-phase high-performance liquid chromatography (RP-HPLC).
The aim of this study was to determine the lipophilicity of arylpiperazinylalkyl derivatives of imidazo[2,1-f]theophylline by RP-HPLC and discuss its influence on affinity to serotonin receptors. The experimental values were also compared with data calculated by means of software packages.
Results obtained in this study can be used in future for optimizing the drug design and synthesis of new tricyclic theophylline derivatives with desired physicochemical properties

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P-55

Solid-Phase Synthesis of Sulfonamide Derivatives of Differently Substituted Alkylamines in the Search for CNS Receptor Ligands.

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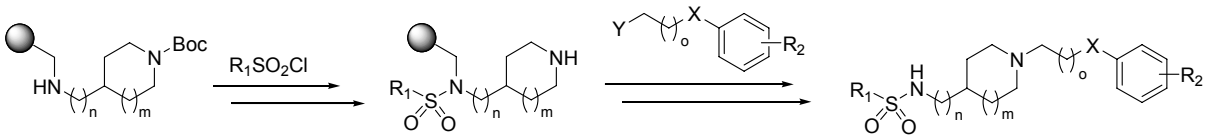
Amine derivatization, widely employed in high-throughput synthesis is highly effective in establishing structure-activity relationships among biologically active compounds targeted on CNS receptors. We recently reported on a solid-phase synthesis (SPS) of arylsulfonamide derivatives of differently substituted arylpiperazines and piperidines as potential dopamine and serotonin receptor ligands [1]. In an effort to expand our SPS technology platform, we sought to develop a robust synthetic route of sulfonamides of piperidines and related pyrrolidines using BAL linker methodology. This approach can potentially take advantage of the commercially available building blocks, and may contain up to six sites of structural diversity (sulfonyl chloride, linker length - *n*, pyrrolidine or piperidine rings, linker length - *o*, and its character, and finally a kind of the alkylating agents).



The reaction manifold, adapted to manual library production using Bill-Board set [2, 3], employed attachment of the primary amine to the BAL resin, sulfonylation of the resin-bound Boc-protected amine, subsequent Boc removal according to Burgess methodology [4], and finally alkylation of the secondary amine.
Presented solid-phase synthetic route enables generation of large combinatorial variations extending the variety of sulfonamide derivatives available for the development of CNS acting agents. This methodology may be applied for the generation virtual libraries to perform virtual screening aiming the selection of the most potent candidates for the synthesis.

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P-56

Kinetic Study of Thymidine and Uridine Radiolysis.

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It is well known that DNA is the main target of radiation in cells. Interaction of different types of radiation with DNA causes adverse biological effects such as mutagenesis and carcinogenesis and at the end result in cell and the whole organism aging. Also understanding of mechanisms of processes occurring during the action of radiation on drugs containing nucleoside fragments is important for assessing stability of these drugs.So the influence of radiation on the nucleic acids components has been so far intensively investigated [1-3].
In our studies gamma radiation initiated processes occurring in aqueous solutions of thymidine and uridine were examined by means of UV spectrometry and chromatography methods. It was found that UV light absorption decreases in irradiated samples. Kinetic study of formation of products generated by radiation was investigated by HPLC. The radiation yields of hydrogen - the main gas product of radiolysis of examined nucleosides were determined by gas chromatography. Reaction rate constants were calculated and mechanisms of investigated processes were proposed.

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P-57

Reactions of Nucleophilic Substitution in Bicyclic Nitroimidazodihydrooxazoles.

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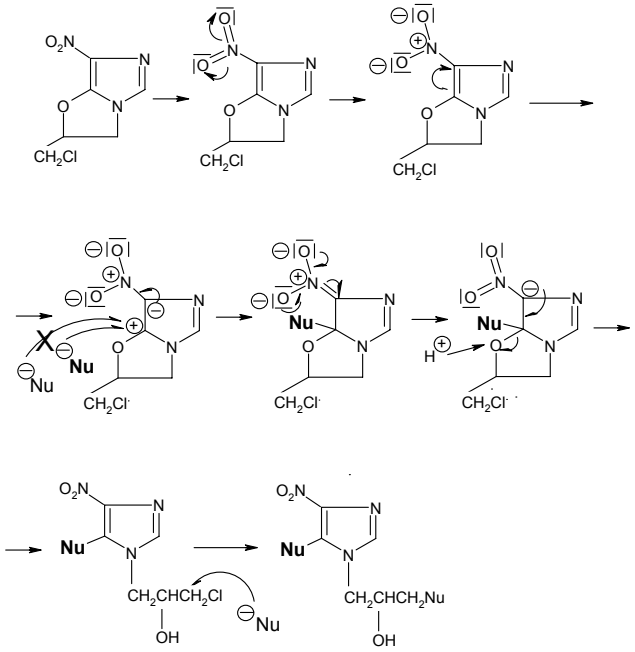
Nitroimidazoles have therapeutic uses as anaerobic antibacterials and antiprotozoal agents [1]. Some bicyclic nitroimidazodihydrooxazoles and nitroimidazotetrahydrooxazines are known as the antituberculosis agents [2].
In our research, there were attempts of the substitution reaction of chlorine atom in 2-chloromethyl-7-nitroimidazo[5,1-*b*]-2,3-dihydrooxazole and its 5-methyl- derivative with nucleophilic compounds, such as: phenols [3], thiophenols, primary and secondary amines. The influence of ratios of substrates, the kind of reaction medium and the polarity of solvent on the kind of formed products were established. On the basis of obtained results, the explanation of mechanism of these reactions was proposed. These reactions probably occure in few steps. Nitro group in nitroimidazodihydrooxazole system has withdrawing effect. It causes the deficit of electrones in the C-5 atom in the imidazole ring. This effect is additionally heightened by the neighbourhood of oxygen atom in dihydrooxazole system. Hence, the C-5 atom is particulary susceptible to nucleophilic attack. When there are two different compounds with nucleophilic properties in the reaction medium, e.g. alcohol and phenol, then more powerful nucleophile attacks the C-5 atom at the imidazole ring. In the aftermath, there is the C-O bond cleavage in dihydrooxazole ring.

Scheme



The negative charge is dislocated on the oxygen atom in the side chain. In the last stage, there is a nucleophilic substitution reaction of chlorine atom with poorer nucleophile e.g. phenoxy group. This step is catalyzed with K_2CO_3. When there is a very strong nucleophile as attacking compound e.g. thiophenol, that is used in 2-fold excess, then this nucleophile substitutes at the C-5 position in the imidazole ring. 4-Fold excess of strong nucleophile additionally causes the substitution reaction of chlorine atom in propyl chain (Scheme).
All of the obtained compounds were tested *in silico* by the *PASS C&T* method. Many of them show interesting pharmacological activi-ties, e.g. antialcoholic, antiinfective, nootropic, antimetastatic, antiproto-zoal properties and many others. Additionally, these products have favorable values of PSA and logP.

Nu – poorer nucleophile,
Nu – stronger nucleophile

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P-58

Attempt for Use of the NMR Spectroscopy in Measurement of the Chemicals Lipophilicity.

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Lipophilicity is one of important parameters characterising molecular properties of chemical substance. Apart of classical method of lipophilicity elucidation based on measurement of partition coefficient between octanol and water there are numerous methods based on chromatography techniques. Due to various limitations of mentioned ways of lipophilicity determination and great importance of this parameter in medicinal chemistry there is still a need for searching of novel methods of its elucidation. It seems that NMR spectroscopy can be used for that purpose as a tool for observation of influence of investigated compound on behaviour of surfactant in water solution. Characteristic property of surfactants is formation in aqueous solutions of so called micelles, which occurs after reaching enough high concentration called critical micelle concentration – CMC. CMC can be varied after addition of other compound into solution due to hydrophobic interactions. More hydrophobic compounds should have bigger affinity to interior of the micelle and this phenomena can induce earlier (for lower concentrations of surfactant) formation of micelles. In our method elucidation of CMC is based on changes of chemical shifts of protons caused by changing of surfactant's molecule neighborhood due to formation of micelle system. Our assumption is, that it is possible to use CMC as a measure of lipophilicity of added compounds.
To confirm this assumption we have investigated the influence of a series of alcohols on CMC of ionic and non ionic surfactants and we have compared the differences in determined CMC values with logP parameter of added alcohols.

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P-59

The Appliance of the Extrapolation Methods Used in Biological Research to Create a Pharmacokinetic Model of Medicaments Isolated From Plants on Example of Codeine.

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The analyse of theoretical biology, mathematical and physical models and bioinformatics tools are more often used in practical medicine. The analysis in silico (i.e. CADD) reduces time and costs of new medicines design and provides wider spectrum of analyse. Moreover, bioinformatics analysis of genome and proteome, especially with the use of microarray allow to specify diagnosis and therapy [1]. Nowadays, the methods enabling precise preparation of therapy by means of correct medicine dosage are being searched. It will allow to increase the efficiency of therapy, reduce or eliminate side effects (i.e. medicine overdosing), reduce the total cost of therapy and shorten its duration.
The elaborated model involves the division of organism into compartments having different physical features (weight and volume) and physiological features (metabolic efficiency, penetration rate of drug). Additional parameters are suggested in the model: $W_{a/b}$, W_{wzb} and λ. Due to it the simulations for individual cases can be run with high precision.
The model is implemented in the GROW_4 virtual environment which is accessible free of charge on the website: www.sitcome.vacau.com

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P-60

Development of *N*-Acryloxysuccinimide-Based Monoliths with Controlled Reactivity for Analytical Applications.

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Monolithic stationary phases for chromatography have recently attracted an increasing attention. The major advantages of capillary columns containing porous polymer-based monoliths include a wide range of available chemistries, high porosity, low resistance to hydraulic flow, fast mass transfer, and almost no limitation in column diameter and length due to the simplicity of the *in situ* preparation process from liquid precursors [1].

The purpose of the presented work was to prepare and study a functionalizable acrylate-based monolithic columns obtained by the UV-initiated free radical polymerization from mixtures containing *N*-acryloxysuccinimide (NAS), acrylamide (AA) and 2-hydroxyethylmethacrylate (HEMA) as functional monomers. Ethylene dimethacrylate (EDMA) and polyethylene glycol diacrylate (PEGDA) were used as hydrophilic crosslinkers, azobisisobutyronitrile (AIBN) as initiator, toluene and cyklohexanol as porogens. *N*-acryloxysuccinimide as a functional monomer is well known for its reactivity towards proteins and was used to elaborate micro-reactors for proteomics applications [2].

After optimization of the monolithic structure, columns were functionalized through reaction with various amine and the chromatographic performances of the monolithic columns for nano-High-Performance Liquid Chromatography (nano-HPLC) and Capillary Electrokinetic Chromatography (CEC) was investigated. Examples of separation in normal phase chromatography as well as in reversed phase mode were presented. All the chromatographic results indicate a strong dependence of the retention, efficiency and selectivity of the monolithic columns on small variations of mobile phase composition and nature of the grafted selector.

In parallel, immobilization of trypsin on monolithic support was performed. An activity of immobilized enzyme was determined by the amidolytic effect on small peptide substrate *N*-α-benzoyl-*DL*-arginine-*p*-nitroanilide (BAPNA).

All the experimental results show that the developed monolithic stationary phases exhibit interesting potential in terms of control of chemical structure with related functionality and separation applications.

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